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Case Report

Serpentine Supra–venous Hyperpigmentation "Badge of Courage" in Fight Against Cancer: An Brief Review

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Abstract:

Persistent serpentine supra–venous hyperpigmentation (PSSH) describes a hyperpigmentation of the skin overlying peripheral veins with characteristic of underlying vessels that are patent. It has been described most commonly after injection of chemotherapeutic drugs. We describe a 44 year old man with diagnosed case of Ca stomach on FOLFOX based chemotherapy. After the 1st cycle of Chemotherapy he developed serpentine supra–venous hyperpigmentation.

Introduction:

Conventional chemotherapy agents commonly cause infusion–site lesions, such as chemical cellulitis due to drug extravasation and evanescent eruptions.[1] 5–Fluorouracil (5–FU) is a cytotoxic agent used mostly in combination to treat a variety of malignant disorders. Hyperpigmentation is a rare side effect occurring with 5–FU infusions; it has been reported in 2–5% of patients. Various types of pigmentary abnormalities have been reported with 5–FU use such as diffuse hyperpigmentation of the face and palms, macular pigmentary changes on the palms and soles, hyperpigmentation overlying the superficial venous network also called serpentine supra–venous hyperpigmentation (SSH) and persistent supra–venous erythematous eruptions (PSEE).[2]

Keywords: Serpentine Supra–venous Hyperpigmentation, Dermatological toxicity, Fluorouracil

Case report:

44 year old normotensive, diabetic male presented with complaints of decreased appetite, pain in the epigastric region for 2 months. CECT abdomen revealed circumferential wall thickening involving the antro–pyloric region of stomach abutting the body of GB and segment IV b of the liver with loss of the fat plane. Multiple adjacent conglomerated peri gastric periportal and aorto–caval metastatic lymph nodes with periportal nodes encasing the portal veins causing mild luminal narrowing features of chronic pancreatitis. Upper gastro–intestinal endoscopic (UGIE) guided biopsy from the stomach suggestive of poorly differentiated carcinoma. Patient was planned for FOLFOX based palliative chemotherapy.

After the 1st cycle of chemotherapy (FOLFOX) lesions appeared to follow the course of upper limb veins with mild itching without any systemic symptoms on the fourth day of chemotherapy. Later the patient reported that the swelling began in his right hand six days after the chemotherapy infusion, and was associated with tender, itchy, and notably darkened forearm veins. Later he developed serpentine supra–venous hyperpigmentation after peripheral fluorouracil chemotherapy infusion started just above the wrist joint to antecubital fossa without affecting the palm. The hyperpigmentation was without supra–venous erythematous eruptions. (Figure Ia, Ib, Ic) No thrombophlebitis was seen and the veins were patent. His blood counts and biochemical tests were normal. (Figure Id)

Treatment

The peripheral venous route was changed to a central venous route for drug infusion. No active treatment was given, put him under close observation only after dermatologist opinion.

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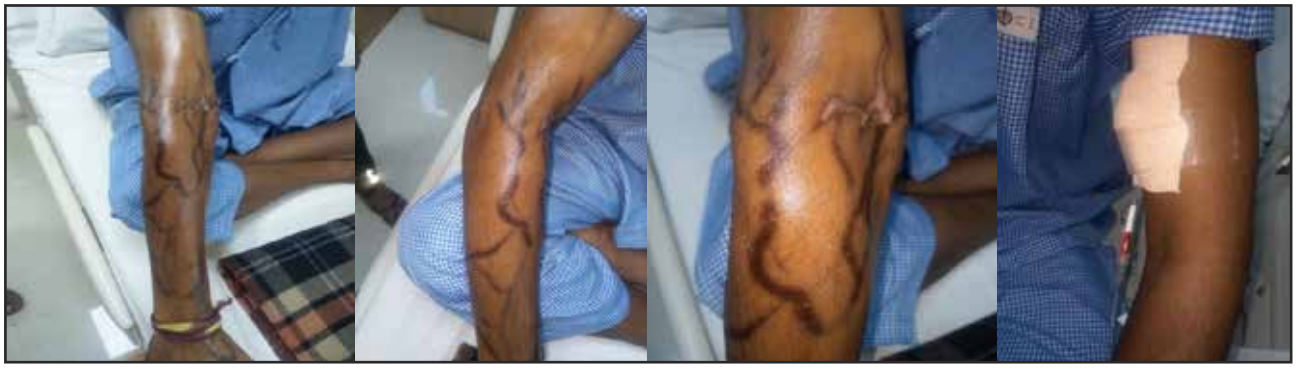

Figure 1: (A–D)Right forearm showing serpentine supra–venous hyperpigmentation

Author$_{(s)}$	Age/ Sex	Drug / Regimen	CT cycle	Diagnosis	Skin reactions
Moertel et al [5] (1969)	ND	5–FU	ND	ND	SSH
Hum & Bateman [6] (1975)	ND	5–FU	5th / 6th cycle	Gastroenteric carcinoma	SSH
Hrushesky [7] (1976, 1980)	56/M	5–FU	18th cycle	Adenocarcinoma of Prostate	SSH
Koehn & Balizet [8] (1982)	19/M	Dacarbazine	4th cycle	Hodgkin's Lymphoma	PSEE
Spencer [9] (1984)	71/M	Mitomycin, 5–FU	2nd cycle	Small cell lung cancer	PSEE
Fine & Breathnach [10] (1986)	57/M 56/M	Broxuridine	2nd cycle 1st cycle	Astrocytoma	PSEE
Arias et al [11] (1991)	64/M	Vinblastine	1st cycle	Small cell lung cancer	PSEE
Claudy et al [12] (1992)	43/M 46/M	Fotemustine	2nd cycle 1st cycle	Malignant melanoma	SSH
Cecchi et al [13] (1994)	60/M	Vinorelbine	3rd cycle	SCC of lung	SSH
Schulte–Huermann et [14] al (1995)	44/M	CHOP	3rd cycle	Large cell lymphoma	SSH
Baselga et al [15] (1996)	7/M 15/M	Cyclophosphamide Doxorubicin	Conditioning to BMT 6th cycle	ALL Hodgkin's lymphoma	SSH
Pujol et al [16] (1998)	47/M	5–FU	1st cycle	SCC of Hypopharynx	PSEE
Marcoux et al [17] (2000)	15/M	Actinomycin & Vincristine	1st Cycle	Para testicular Rhabdomyosarcoma	SSH
Ayodgan et al [4] (2005)	47/M	Docetaxel	1st cycle	SCC of Lung	PSEE
Marongiu et al [18] (2009)	85/M	Vinorelbine	___	Recurrent classic Kaposi's sarcoma	SSH with PSEE
Geddes et al [19] (2010)	45/F	5–FU (FEC)	1st cycle	Ca Breast	SSH
Lancman et al [20] (2018)	50/M	R–CHOP	1st Cycle	DLBCL	SSH
Narayan et al (2021) Present study	44/M	5–FU (FOLFOX based regimen)	1st Cycle	Ca Stomach	SSH

Table 1: Various chemotherapeutic agents reported till date for Serpentine Supra–venous Hyperpigmentation and Persistent Supra–venous erythematous eruptions

Duration of onset (days)	Preceding erythema	Distal involvement	Duration (days)	Skin biopsy
ND	ND	ND	ND	ND
ND	ND	ND	ND	ND
ND	ND	ND	ND	ND
1	Erythematous plaques, ulceration	In vicinity	21: Recurrence	EM–Like
<30	Erythematous papules	No	ND	EM–Like
2 10	Erythematous papules	Generalized exfoliative erythroderma	14 ND	Sparse dermal infiltrate; focal melanin incontinence No
1	Erythematous papules, plaques, vesicles, bullae	No	14: No recurrence	EM–Like
ND	ND	No	60	↑ Melanization of basal layer and of melanophages; no dermal infiltrate
24	ND	No	ND	↑ Melanization of basal layer and of melanophages; no dermal infiltrate
30	ND	Nails	ND	ND
180	ND	ND	ND	ND
4	Linear	Macules, plaques, trunk, legs	90	EM–Like
1	Macular and Linear (discrete)	No	300	↑ Melanization of basal layer; sparse dermal infiltrate; few melanophages; neutrophilic hidradenitis
2	Erythematous eruption	No	180	↑ Melanization of basal layer; with upper dermis, lymphoplasmocytic infiltration around the dilated vessels
1	Erythematous changes	No	ND	ND
–––	ND	No	ND	ND
6	ND	No	ND	ND
4	Macular and Linear	No	ND	ND

Outcome and follow–up

The patient was regularly followed in every 2weeks. 5–FU in the same dose was continued through the central port every 14 days. These lesion started resolving in a span of approximately in 4th week, evolving into hyperpigmented streaks with mild scaling.

Discussion:

Serpentine supra–venous hyperpigmentation (SSH) was the term coined by Hrushesky in 1976 in association with 5–FU.[3] PSSH is a rare and poorly understood vasculo–cutaneous entity usually presenting in the setting of recent chemotherapy infusion. The lesions usually

develops within 24 hours to 15 days after intravenous cytotoxic drug infusion and subside spontaneously after 1–3 weeks often leaving residual hyperpigmentation. [4] The pathogenesis of the serpentine supra–venous hyperpigmented changes can be attributed to the 5–FU induced loss of endothelial integrity of the blood vessels causing leakage of drug into epidermis, thereby damaging the packing of melanosomes within the keratinocytes. [2] Due to such mechanism adequate venous washing may mitigate or prevent the PSSHE by reducing the toxic load in the veins. Cytotoxic damage and hypersensitivity reactions both contribute to pigmentary changes secondary to subclinical phlebitis. Due to hypersensitivity reactions, other sites far from the vicinity of the infusion site may develop similar changes. Depletion of tyrosinase inhibitors, resulting in increased hyperpigmentation and direct toxic effect on epidermal melanocytes are also few other mechanisms of these dermatologic changes.

Various chemotherapy drugs including alkylating agents, anti–tumour antibiotics, anti–microtubules, and proteasome–inhibitors have also caused this distinctive pattern of pigmentation.[4] There are also few other drugs like multibacillary regimen in the form of minocycline also reported PSSHE in lepromatous leprosy patient.

Management consists of recognition of associated complications, risk and symptomatic treatment; a Doppler ultrasound can be performed if there is suspicion for thrombophlebitis.

Conclusion:

Treatment with the associated drug may be continued since this adverse reaction is benign and self–limiting. Physicians must learn to promptly recognise this rare side effect of this commonly used chemotherapeutic agent So that timely action is taken without much delay in treatment and without any dose modifications.

Competing interests: The authors have no conflicts of interest to disclose.

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