CASE REPORT

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Hyperpigmentation – A Clue for Diagnosis

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Abstract

Hyperpigmentation is a condition that causes the skin to darken. It can occur in small patches, cover large areas, or affect the entire body. Hyperpigmentation may be the sign of an underlying benign or malignant condition. This article presents adult patients with increased pigmentation and reviews various underlying causes. Case series of 8 patients presenting in Department of General Medicine with complaints of hyperpigmentation were reviewed. Data of symptoms and lab investigations were collected.

Key words: Hyperpigmentation, Addison's disease, Hand Foot Syndrome, CREST Syndrome, Mixed Connective Tissue Disorder.

Cases series

Case 1

A 59-year-old male came with complaints of pigmentation of skin and mucus membranes, apathy and easy fatigability since 7 months. On examination, the patient had generalised pigmentation of the face, upper limbs and lower limbs involving palms and soles. Oral mucosa was pigmented and tongue was darkly pigmented (Fig. 1a). On evaluation, the patient had hypotension, generalised

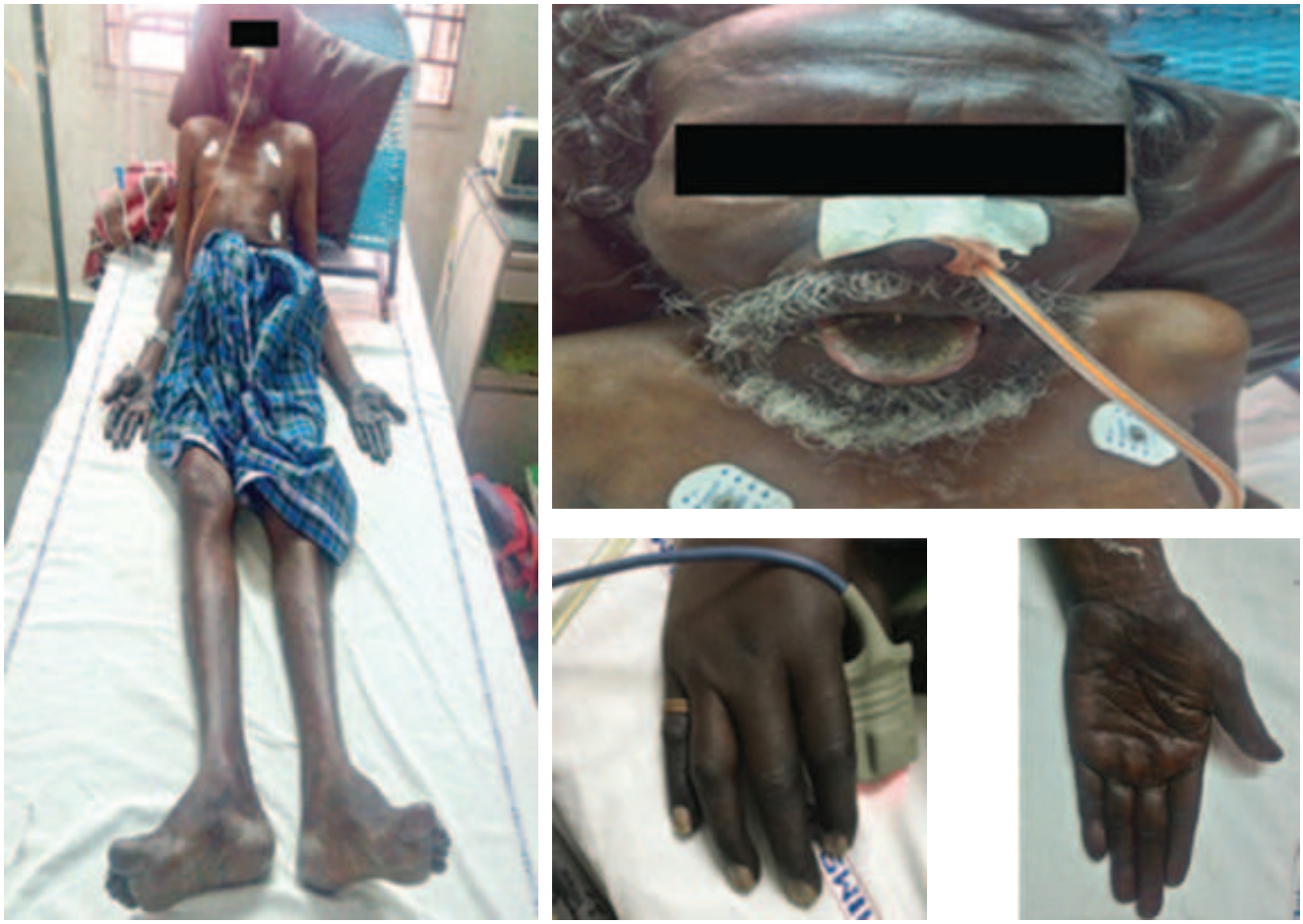

Fig. 1a: *On admission.*

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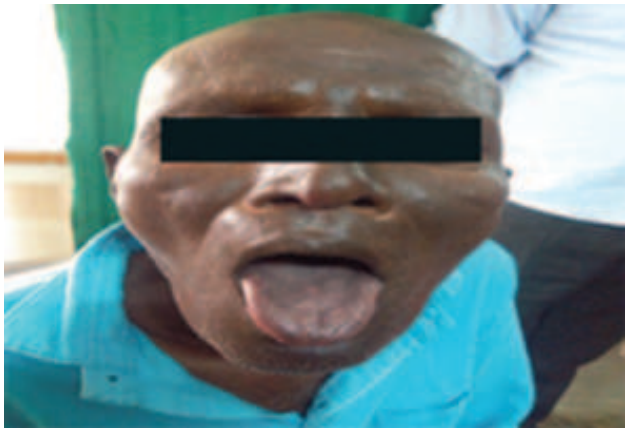

Fig. 1b: *After 1 month of treatment.*

Fig. 1c: *After 2 months of treatment.*

weakness and hypoglycaemia (random blood glucose: 56 mg/dl). Investigations revealed eosinophilia (E - 40%), hyponatraemia (120 mmol/l), hyperlakaemia (5.2 mmol/l) and serum cortisol levels were 0.1 mcg/dl. Imaging showed bilateral enlarged and calcified adrenals. X-ray chest was normal.There was no cervical lymphadenopathy. Patient was diagnosed as having Addison's Disease. The patient was managed in the intensive care unit with all supportive therapy and corticosteroids. Patient recovered well within 4 weeks and was discharged on oral steroids (Fig. 1b). At follow-up after 2 months, he was doing well and his pigmentation had subsided (Fig. 1c).

Case 2

A 55-year-old female came with hyperpigmentation of face, and knuckles, tingling sensation of the feet and easy fatigability. On examination, patient had pallor, bald tongue, pigmentation of the knuckles and palmar creases (Fig. 2). Romberg's test was positive. On evaluation haemoglobin was 5.4 gm%, MCV was 108 fl and serum B_{12} level was 145 pg/ml. Peripheral smear showed macrocytes with hypersegmented neutrophils. Patient was diagnosed with megaloblastic anaemia. Patient was treated with folic acid and cyanocobalamin supplementation and symptoms improved gradually.

Fig. 2: *bald tongue, pigmentation of the knuckles and palmar creases.*

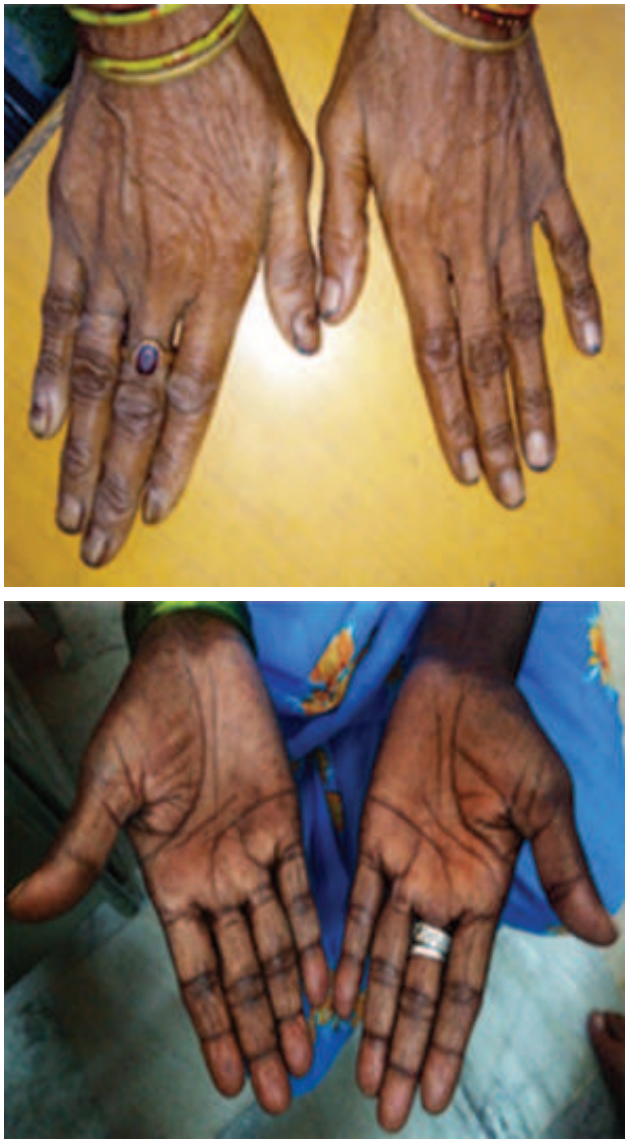

Fig. 2: *Bald tongue, pigmentation of the knuckles and palmar creases.*

Case 3

A 42-year-old hypertensive and diabetic patient was diagnosed as CKD stage V, 2 years back, and was on maintenance haemodialysis. Patient started to notice pigmentation of face, upper limbs and lower limbs for the past 8 months (Fig. 3). There was no history of pruritius. Patient had pallor, no jaundice and no pedal oedema. On evaluation he had haemoglobin of 10 gm%. Peripheral smear showed microcytic hypochromic anaemia. LFTs were normal. RFTs showed blood urea of 39 mg/dl and serum creatinine of 3.6 mg/dl. Patient was diagnosed as CKD-induced hyperpigmentaion.

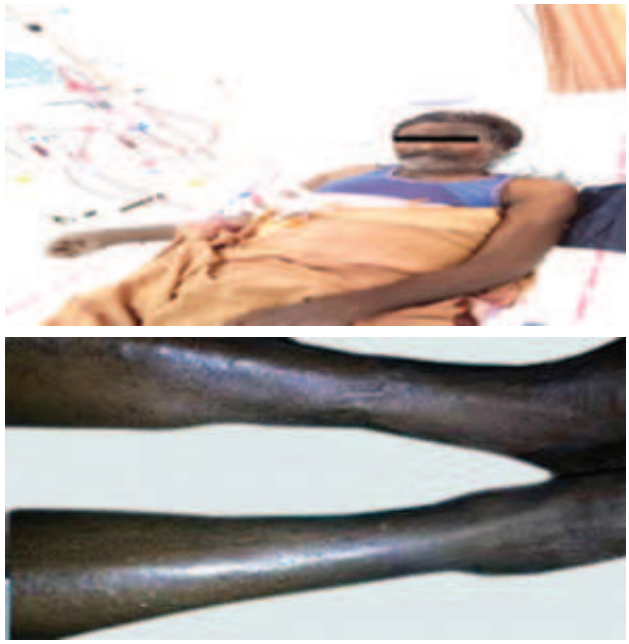

Fig. 3: *Pigmentation of face, upper limbs, and lower limbs.*

Case 4

A 60-year-old chronic gutkha chewer presented with history of hoarseness of voice and difficulty in swallowing for the past 6 months. On evaluation patient was diagnosed to have laryngeal carcinoma with nodal metastasis. Patient was subjected to concomitant chemo-radiotherapy cycles following which he developed hyperpigmentation and scaling of the neck and cheeks (Fig. 4). Patient was diagnosed to be having acute radiation dermatitis.

Fig. 4: *Hyperpigmentation and scaling of the neck and cheeks.*

Case 5

A 56-year-old female came with history of abdominal distension, easy fatigability, decreased appetite and pigmentation of the face, extremities and the trunk since 6 months (Fig. 5a). Patient had multiple painful erythematous nodulated lesions over the lower limbs suggesting erythema nodosum (Fig. 5b). On evaluation, patient had hepatosplenomegaly, ascites, and cervical lymphadenopathy. Blood routine investigations revealed anaemia with WBC counts of 85,000 per cubic mm with blast forms in the peripheral smear. On further investigations with cytogenetics, patient was diagnosed as acute myeloid leukaemia (AML-M5).

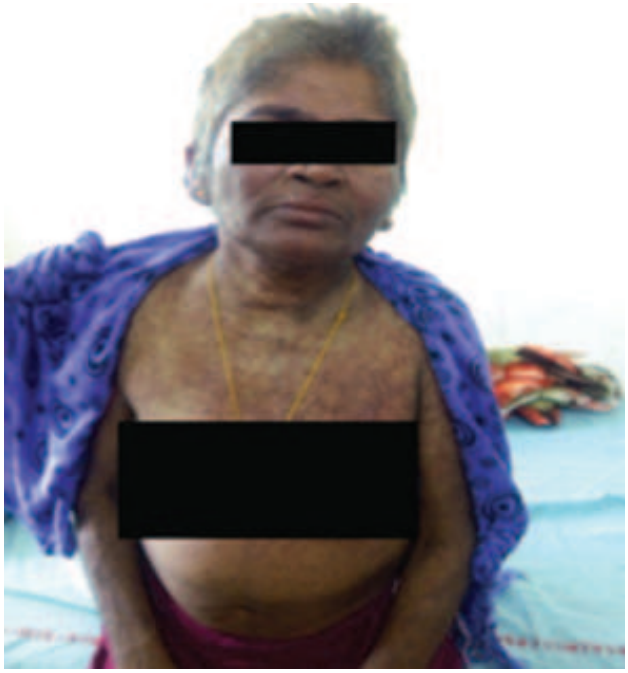

Fig. 5a: *Pigmentation of the face extremities and the trunk.*

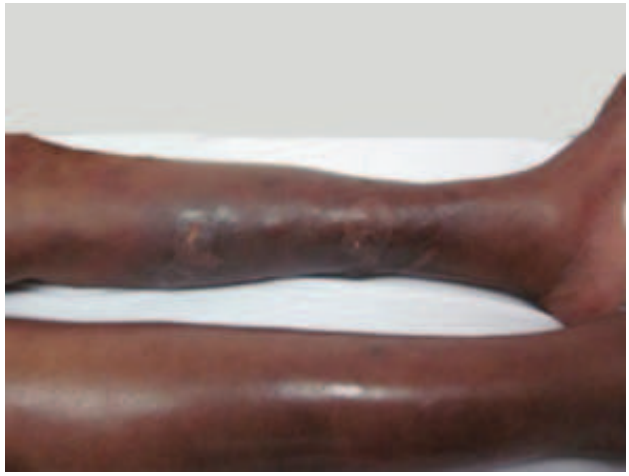

Fig. 5b: *Erythema nodosum.*

Case 6

A 50-year-old male patient came with complaints of hyperpigmentation of the palms and dorsum of the hands for 2 months (Fig. 6). He was a diagnosed case of adenocarcinoma of stomach stage IV with liver metastases

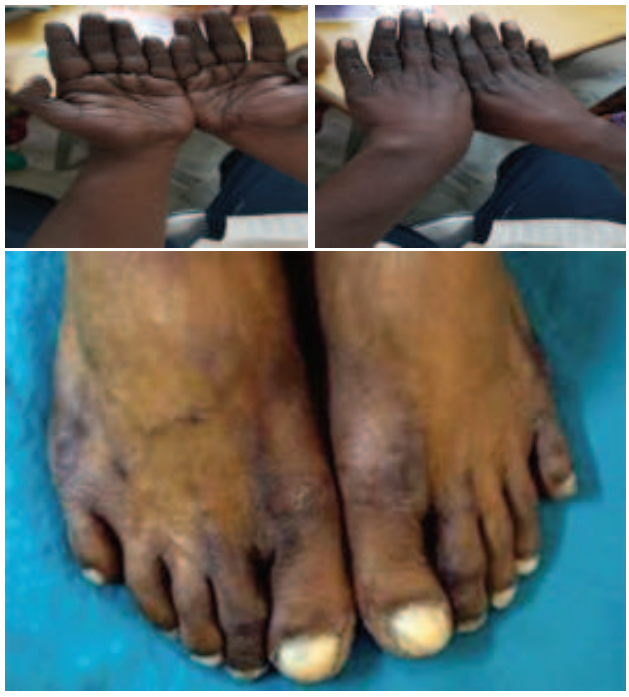

Fig. 6: *Hyperpigmentation of the palms and dorsum of the hands.*

4 months back. He was on palliative chemotherapy with capecitabine. Patient developed pigmentation following 3 cycles of chemotherapy. There was no pruritus and photosensitivity. Patient was diagnosed as having "Hand Foot Syndrome" – a side-effect of capecitabine.

Case 7

A 23-year-old male presented with complaints of tightening of skin over extremities and chest since 1 year. He complained of multiple hyper- and hypo-pigmented areas over trunk and waist. He had difficulty in swallowing, multiple joint pains. On examination, patient had salt and pepper pigmentation on nape of neck and chest (Fig. 7a). Digital tip ulcerations and sclerodactyly were present (Fig. 7c). Subcutaneous nodules in the skin over the lateral aspects of bilateral hips were seen. Investigations showed ESR 45 mm after 1 hour. Barium swallow imaging showed narrowing of lower end of oesophagus (Fig. 7b). ANA profile showed anti Scl70 - positive (+++). Patient was diagnosed as having CREST Syndrome.

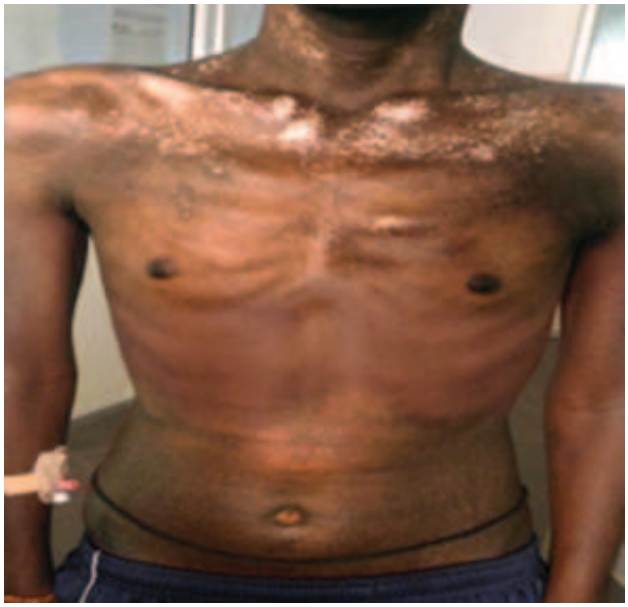

Fig. 7a: *Salt and pepper pigmentation.*

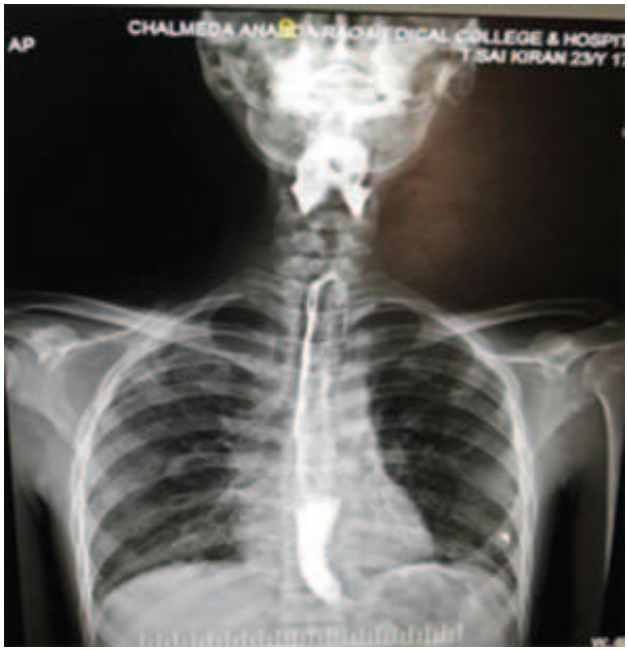

Fig. 7b: *Narrowing of lower end of oesophagus.*

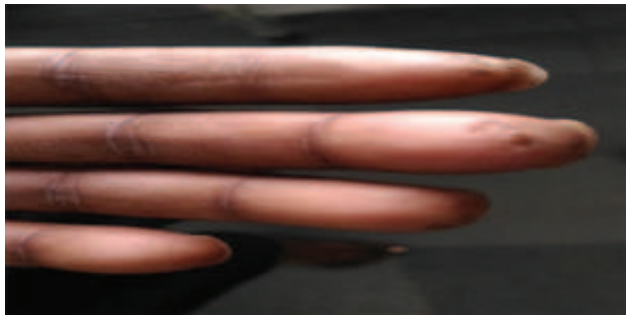

Fig. 7c: *Digital ulcers.*

Case 8

A 32-year-old male patient, construction worker by occupation came with complaints of severe body pains, low backache, difficulty in walking and patches of hyper and hypo pigmentation over the nape of neck, chest wall, trunk, fingers of hands and over the lower limbs since 1 year (Fig. 8b and 8c). Patient had difficulty in opening the mouth. Patient had no addictions. On examination, patient had coarse and shiny skin with salt-pepper pigmentation (Fig. 8c). Skin pinch was normal. Butterfly shaped pigmentation was present over the face and there was no photosensitivity (Fig. 8a). Contractures of the digits of hands and feet were seen. There was no

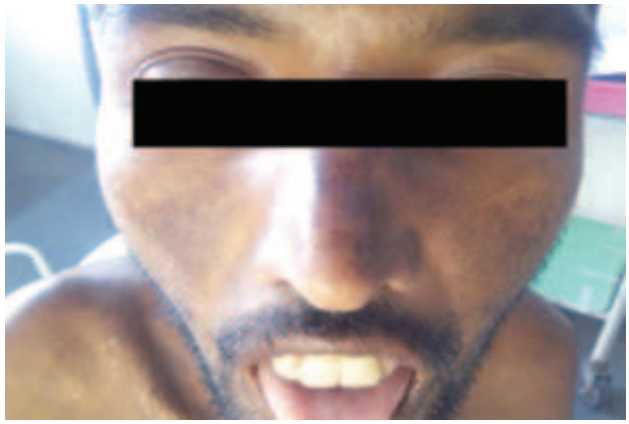

Fig. 8a: *Butterfly pigmentation.*

difficulty in swallowing of solids and liquids. There were no ulcerations over the tips of the digits. There were no subcutaneous nodules. There was pallor, jaundice, but no pedal oedema. Investigations showed haemoglobin of 9 gm%, ESR of 120 mm for 1st hour, direct and indirect Coombs test were positive. Peripheral smear showed schistocytes. Sickling test was negative. RA factor negative, LFT showed total bilirubin of 5.6 mg/dl (D:1.6; ID:4.0) and RFT was normal. USG abdomen showed borderline hepatosplenomegaly. ANA profile was U_1 RNP positive (3+). Patient was diagnosed as Mixed connective tissue disorder (MCTD).

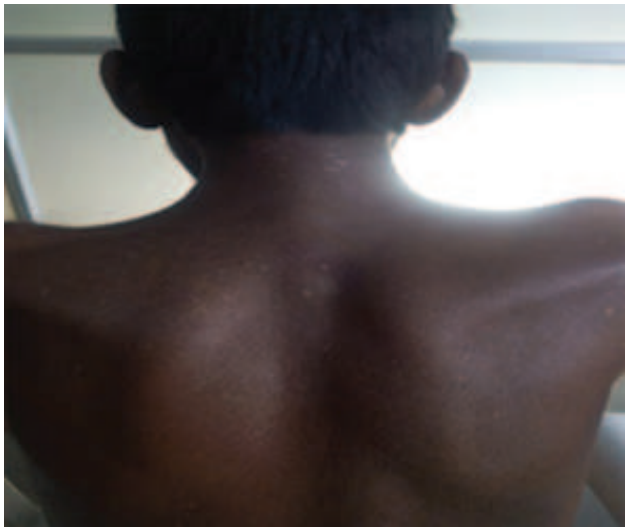

Fig. 8b: *Pigmentation over the nape of neck.*

Fig. 8c: *Salt-pepper pigmentation.*

Discussion

A variety of pathological processes may cause Addison's disease, which was first described by Thomas Addison[1]. The commonest causes of Addison's disease are autoimmune and tuberculosis. Several autoimmune processes can lead to adrenal insufficiency affecting exclusively the adrenal glands or be the part of a more complex inherited autoimmune polyglandular syndrome. Tuberculosis is the most common cause of Addison's disease in developing countries. One of the hallmark signs of Addison's disease is cutaneous and mucosal hyperpigmentation related to ACTH melanogenesis action[2]. Pigmentation can be homogeneous or blotchy. The pigmentation may involve skin, oral cavity, conjunctiva, and genitalia. This case was managed by methylprednisolone initially, and recovered after brief hospitalisation. The patient is now maintained with methylprednisolone.

In patients with vitamin B12 deficiency, the following skin lesions are reported: skin hyperpigmentation, vitiligo, hair changes, and recurrent angular stomatitis. Hyperpigmentation of the extremities – especially over the dorsum of the hands and feet, with accentuation over the interphalangeal joints and terminal phalanges – associated with pigmentation of oral mucosa is characteristic of vitamin B12 deficiency. The mechanism of hyperpigmentation is due to increased melanin synthesis rather than a defect in melanin[3].

In renal failure patients, diffuse hyperpigmentation is attributed to an increase in melanin in the basal layer and superficial dermis due to failure of the kidneys to excrete beta-melanocyte-stimulating hormone (β-MSH). Hyperpigmented macules on the palms and soles have been reported by Pico *et al*. and are also attributed to increased circulating β-MSH[4]. Hyperpigmentation in sun exposed areas is a common finding in CKD patients. Luqman *et al*[5] reported hyperpigmentation in 44% of their CKD patients on dialysis. Hyperpigmentation was more commonly found in patients who had longer duration of CKD and also in patients receiving haemodialysis.

Acute cutaneous skin reactions are common side-effects of radiotherapy. Acute radiation dermatitis is one of the most common reactions to radiotherapy and usually occurs within 90 days of exposure. The severity of reaction ranges from mild erythema to moist desquamation and ulceration. The reaction typically starts within 1 - 4 weeks after starting radiation treatment, and persists during the radiation treatment period[6]. Acute radiation dermatitis is likely to heal with mild cutaneous changes. Acute reactions start with erythema, oedema, pigmentary changes and depilation that correlate with the amount of radiation exposure. Dry desquamation can be treated with hydrophilic moisturisers, while pruritus and irritation can be treated with low to mid potency steroids.

Acute leukaemia has been associated with a variety of cutaneous inflammatory lesions. The cutaneous manifestations may be specific by leukaemic infiltration or may be non-specific. The non-specific lesions include mucositis secondary to chemotherapy, haemorrhagic manifestations secondary to homeostasis disturbances and infections due to immunosuppression. Paraneoplastic cutaneous syndromes are rarely observed (erythema multiforme, leukocytoclastic vasculitis, pyoderma gangrenosum, Sweet syndrome and erythema nodosum). In our case, we report satellite cutaneous manifestations, i,e., erythema nodosum described in leukaemia. Usually, the erythema nodosum precedes leukaemia by 1 to 12 months, but it could occur during the evolution of this malignancy[7]. Specific treatment of leukaemia had allowed the recovery of erythema nodosum.

Capecitabine is a systemic prodrug of 5-fluorouracil (5 FU) which is currently FDA approved for use as adjuvant therapy in colorectal cancer and gastric cancer. Capecitabine as compared to 5FU has the added advantage of oral administration making it expedient in a home-based setting, thereby minimising the need for venous access as well as hospital stay. Hand Foot Syndrome (HFS) is a dose limiting adverse effect of capecitabine. Certain theories suggest that capecitabine may be eliminated by the eccrine glands, the resulting excretion causing HFS, since the hands and feet have an increased number of eccrine glands[8]. Some theories even suggest that it is the result of an inflammatory reaction due to over-expression of COX-2. Treatment of capecitabine induced HFS is immediate discontinuation of the drug and supportive measures to reduce pain and to prevent secondary infection. On resolution of symptoms, the drug is restarted at the same dose or reduced dose depending on the severity and frequency of the adverse effect. Proper patient education by the treating physician prior to the start of medication and early recognition of symptoms can help in preventing/minimising this adverse effect.

Scleroderma is an autoimmune disease in which the antibodies target blood vessels and connective tissues. Resorption of the terminal phalanges, short and claw-like fingers because of acro-osteolysis, ulcers on finger tips are common in patients with scleroderma. Trismus, widening of the periodontal space, decrease in facial wrinkles owing to fibrosis of skin, orofacial telengiectasia, hyperpigmentation are some of the changes which may occur. The salt-and-pepper appearance is characterised by the presence of vitiligo-like depigmentation with perifollicular pigmentary retention[9]. The rich capillary network surrounding the hair follicle preserves melanogenesis, and hence the retained perifollicular pigmentation in systemic sclerosis[9].

Mixed connective tissue disease (MCTD) is a specific condition in which two or more connective tissue disorders are associated with the presence of antibody against a specific uridine-rich U1 ribonucleoprotein (U1RNP). Clinical manifestations are usually those of systemic lupus erythematosus (SLE), scleroderma and inflammatory myositis. In the study of Sumit Sen *et al*[10], one woman from the MCTD group was noticed with scattered patchy hypopigmentation of the face and fingers with tightened and contracted digits and had generalised hyperpigmentation. The condition is treated by corticosteroids and immunomodulators.

Conclusion

Hyperpigmentation can be a presenting symptom of a spectrum of diseases which range from benign reversible conditions like vitamin deficiencies, drug-induced pigmentation to life threatening conditions like malignancies and as a consequence of cancer treatment. So any patient with complaints of hyperpigmentation needs to be thoroughly evaluated for the underlying cause and for appropriate management.

References

1. Grossman AB. Thomas Addison and his disease. *Grand Rounds* 2004; 4: L8-9.
2. Stewart PM, Krone NP. The adrenal cortex. In: Kronenburg HM, Melmed S, Polonsky KS *et al* editors. Williams Textbook of *Endocrinology*. 12th ed. Philadelphia PA: Saunders Elsevier 2011; 15: 515-20.
3. Mori K, Ando I, Kukita A. Generalised hyperpigmentation of the skin due to vitamin B12 deficiency. *J Dermatol* 2001; 28 (5): 282-5.
4. Pico MR, Lugo-Somolinos A. Cutaneous alterations in patients with chronic renal failure. *Int J Dermatol* 1992; 31: 860-3.
5. Luqman N, Khalid M, Shaheen JA. Cutaneous manifestations of chronic renal failure in Bahawalpur, Pakistan. *J Pak Assoc Dermatol* 2012; 22 (3): 219-23.
6. Bolderston A, Lloyd NS, Wong RK *et al*. Supportive Care Guidelines Group of Cancer Care Ontario Program in Evidence-Based C. The

prevention and management of acute skin reactions related to radiation therapy: a systematic review and practice guideline. *Support Care Cancer* 2006; 14 (8): 802-17.

7. Sullivan R, Clowers-Webb H, Davis MD. Erythema nodosum: a presenting sign of acute myelogenous leukaemia. *Cutis* 2005; 76: 114.
8. Schellens JHM. Capecitabine. *The Oncologist* 2007; 12 (2): 152.
9. Rai VM, Balachandran C. Pseudovitiligo in systemic sclerosis. *Dermatol Online J* 2005; 11: 41.
10. Sumit Sen *et al*. Cutaneous Manifestations of Mixed Connective Tissue Disease: Study from a Tertiary Care Hospital in Eastern India. *Ind J Dermatology* 2014; 59 (1): 35-40.