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VARIED , UNPRECEDENTED DERMATOLOGIC MANIFESTATIONS OF HYPOVITAMINOSIS D ---A CASE SERIES

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ABSTRACT
Hypovitaminosis D is endemic in India . Hypovitaminosis D not only results in musculoskeletal disorder , but also affects extra skeletal system . In this article ,we describe three interesting patients of erythema nodosum , heel fissures and palmar hyperhidrosis with hypovitaminosis D , responded well to treatment with vitamin D , which has not been reported earlier .

INTRODUCTION
Hypovitaminosis D is endemic in India , with a prevalence of around 70 -100 % [1]. Hypovitaminosis D deficiency is most under-diagnosed and under -treated nutritional deficiency in the world [2,3,4]. The source of Vitamin D is primarily from skin through synthesis on exposure of ultraviolet –B rays from sun . More home boundedness with mobile phones in hand and less exposure to sunlight , cultural and social taboos dictating lifestyle patterns such as clothing , vegetarianism in most Indians and reduced vitamin D synthesis in dark skinned people are the main reason for rising prevalence of hypovitaminosis D . Hypovitaminosis D not only results in musculoskeletal disorder , but also affects extra skeletal system [5,6]. Here , we report three undescribed dermatogic manifestations of hypovitaminosis D .

CASE REPORT
CASE 1 : A 49 years , female in government service was hospitalized in august ,2016 with severe generalized muscle pain , vomiting , anorexia , fever , malaise , joint pain and multiple 1-2 cm , painful and nodular swellings on the both sole of feet for 3-4 days . She had history of recurrent episodes of similar swellings in past for 3 years preceding to this event and these swellings subsided each time with a course of antibiotics and analgesics , which was diagnosed as idiopathic erythema nodosum by treating physician . She was also complaining of recurrent headache in past , diagnosed as chronic tension headache and had relief with flunarazine . On examination she was conscious , pulse 110/min, blood pressure 140/90 mm of Hg and systemic examination did not reveal any abnormality . On investigation complete blood count, kidney and liver function test , sugar (fasting) , lipid profile , uric acid , calcium , phosphorus levels in blood , electrocardiogram , chest skiagram and computerized tomographic scan of thorax were normal . The ultrasonography of whole abdomen showed cholelithiasis, thyroid stimulating hormone level was mildly raised (8.2 IU/ml)with normal free T4 level and serum vitamin D level was very low (10 ng/ml) . She was treated during hospitalization with intravenous fluid , injection pantoprazole , ondansetron , paracetamol infusion and amoxicillin- clavulinic acid . Cholecalciferol 60000 U orally once weekly was started and continued for 10 weeks followed by once monthly maintained for past four years and her follow up vitamin D level was normal during that period . She did not suffer from a single episode of erythema nodosum lesion during past four years till January ,2021. She was also receiving levothyroxin 25 gm/day .

CASE 2
A 50 years female , homemaker attended out patient department with complaint of generalized aches and cracked heel in the month of December , 2017 . She observed these cracked heel during winter months each year . On examination her pulse was 84/ min , blood pressure was 128/84 mm of Hg and systemic examination did not reveal any abnormality . On investigation complete blood count , sugar (F) , lipid profile , kidney and liver function test , calcium and phosphorus , chest skiagram , electrocardiogram and ultrasonography of whole abdomen were normal .Her vitamin D level was low (14 ng/ml) . She received treatment with paracetamol 1000mg thrice daily and oral cholecalciferol 60000U every week for 10 weeks followed by once monthly continued for past three years to maintain the normal vitamin D level . On follow up , she did not notice cracked heel during winter months of past three years .

CASE 3
A 22 years , male student with complaint of multiple 1-3 mm pustulonodular lesions over face and upper trunk and excessive sweating over both palm in May 2019 . On physical examination no abnormality was detected . His complete blood count , sugar (F) , kidney and liver function tests , thyroid stimulating hormone level were normal , but vitamin D level was below normal level (19 ng/ml) . A course of oral doxycycline , topical retinoids and oral cholecalciferol in a dose of 60000 U week for 10 weeks was given . Cholecalciferol was continued once monthly and excessive palmar sweating subsided .

Proper written informed consent was taken from all three patients to publish this article .

DISCUSSION

Human beings obtain a adequate amount of vitamin D either from adequate exposure of the skin to sunlight or from their diet . Vitamin D exists in two forms namely vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Vitamin D_3 is produced in the skin on exposure to sunlight and is found in animal food sources e.g., fatty fish (e.g., salmon, mackerel and tuna), cod liver oil, milk, *etc*. The source of Vitamin D_2 is from sun-exposed yeast and mushrooms. Vitamin D (both forms D_3 or D_2) is a prohormone which requires two hydroxylations . The first hydroxylation occurs in the liver to form 25-hydroxyvitamin D, also known as 25(OH)D or calcidiol. The second hydroxylation occurring primarily but not exclusively in the kidneys to form 1,25$(OH)_2$D, also known as calcitriol. This active form of vitamin D [1,25$(OH)_2$D] is released in blood, reaches its target tissues to exert its endocrine functions through the vitamin D receptor (VDR) . Vitamin D deficiency is defined as 25(OH)D < 20 ng/mL, insufficiency as 20–29 ng/mL and sufficiency as ≥30 ng/mL[1] . Musculoskeletal pain , recurrent erythema nodosum, chronic tension headache , subclinical hypothyroidism , cholelithiasis and vitamin D deficiency was the clinico- biochemical abnormality in first patient of this study . Chronic tension headache and musculoskeletal pain in vitamin D deficiency has been described in literature [7,8] . After the normalization of serum vitamin D levels , the patient has not suffered from even a single episodes of erythema nodosum lesion during past four years . Erythema nodosum is the most common form of panniculitis (inflammation of subcutaneous fat tissue)and occurs three to five times more often in females [9]. In this study , the patient was also a female .Typically erythema nodosum appears as erythematous painful round nodules , located on the anterior surface of the leg , but can spread to other areas of body . Unlike this typical site of lesion , it was present on sole of both foot in patient of present study .The episodes of erythema nodosum lesion may be accompanied by systemic symptoms such as fever , malaise and arthralgia . All of these symptoms were present during last episode in patient of present study .The lesions of erythema nodosum usually resolve spontaneously within 2-8 weeks without leaving scars . The most common causes are infections (28-48%), sarcoidosis (11-25%) , drugs (3-10%) , pregnancy (2-5%) and enteropathies (1-4 %) [9] . However , in many cases it is impossible to determine the cause (idiopathic)[10] . The recurrent erythema nodosum with elevated markers of inflammation , may be the only manifestation of vasculitis [9] . Vitamin D3 , the active form of vitamin D , not only regulates calcium and bone metabolism but also plays an immunomodulatory role mediated through binding of its receptor (VDR) in monocytes , macrophage and activated lymphocytes [11] . It has also been observed that individual with a type 2 lepra reaction associated with neuritis and or erythema nodosum leprosum had very low vitamin D receptor on RNA expression along with low vitamin D levels in blood[11] . So, recurrent erythema nodosum in first patient of the present study was probably due to unregulated immune expression of hypovitaminosis D .

The second patient in present study had the problem of cracked heel , also known as heel fissures and vitamin D deficiency . With correction of vitamin D deficiency , there was healing of heel fissures and subsequently it did not recur. Heel fissures are a common cosmetic problem . Dry and thick skin on the bottom , outer edge of the heel with increased pressure on the fat pad results in skin to split that can manifest with pain and bleeding . The other factors for heel fissures are obesity , wearing open heel footwear such as sandals and exposure to cold weather . The active vitamin D locally produced in skin is involved in epidermal differentiation and proliferation , wound response and tumorigenesis [12]. The hypovitaminosis D in second patient of present study could be a contributory factors in persistent and recurrent heel fissures .

The relief from the problem of palmar hyperhidrosis following correction of vitamin D deficiency was observed in third patient of present study . Although direct relation of vitamin D and sweat production was not found after through literature search ,the role of calcium as a important link in the process of stimulus –secretion coupling and stimulus permeability coupling has been demonstrated for a variety of exocrine glands [13,14,15]. So, there may be some indirect control over sweat production by vitamin D through calcium .

CONCLUSION

The erythema nodosum , heel fissures and palmar hyperhidrosis in vitamin D deficiency has not been described in literature . The novelty of this findings in a common deficiency disorder of vitamin D inspired us to publish this article . Future large – scale studies are needed to establish these relations.

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