CASE REPORT

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Redundant plantar skin folds

LAURA OTILIA DAMIAN[1)], SIAO-PIN SIMON[2)], IOANA FELEA[1)], CAROLINA BOTAR-JID[3)], BOGDAN STANCU[4)], LILIANA ROGOJAN[5)], CRISTINA ANA MARIA PAMFIL[2)], ADRIANA ALBU[6)], SIMONA REDNIC[2)]

[1)]*Department of Rheumatology, Emergency County Hospital, Cluj-Napoca, Romania*
[2)]*Department of Rheumatology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*
[3)]*Department of Radiology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*
[4)]*2nd Department of Surgery, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*
[5)]*Department of Pathology, Emergency County Hospital, Cluj-Napoca, Romania*
[6)]*2nd Department of Internal Medicine, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

Abstract

A 46-year-old female patient presented with photosensitivity, symmetric arthritis, episodic plantar pain and strikingly redundant plantar skin folds, likely due to lipoatrophy after recurrent episodes of plantar panniculitis. In this context, leukopenia with lymphopenia, thrombocytopenia and positive antinuclear antibodies were revelatory for systemic lupus erythematosus. However, a small cerebriform plantar collagenoma, along with discrete dysmorphic features with downslanting palpebral fissures and mild right ptosis, second and third syndactyly and a larger first right toe since childhood, and early-onset bilateral ovarian cystadenoma, suggested a minimal Proteus syndrome. Genetic confirmation could not be performed. As adipose tissue dysregulation may be a feature of Proteus syndrome, the possible mechanisms leading to localized lipoatrophy in this setting are discussed. This case enlights intriguing links between adipogenesis, inflammation and dysmorphology. From a practical point of view, finding and treating an over-imposed inflammation could help limit damage in a hamartomatous syndrome.

Keywords: plantar panniculitis, *cutis laxa*, systemic lupus erythematosus, plantar cerebriform hyperplasia, Proteus syndrome, adipose dysregulation.

Introduction

Plantar panniculitis is a rare condition, consisting in inflammatory sole nodules [1]. Lupus panniculitis may rarely result in lipoatrophy and acquired *cutis laxa* with skin redundancy [2].

Proteus syndrome (PS) is a rare hamartomatous disorder, affecting one in one to 10 million people, due to AKT1 gene mutation [3]. Skin hypertrophy and furrowing, as well as adipose tissue dysregulation with hypo- or hyperplasia, can be part of the PS clinical picture [4]. PS manifests in early childhood with asymmetric and progressive tissue overgrowth: partial gigantism of extremities, hemihyperplasia, hamartomas and cerebriform masses on the palms or soles [3]. Cerebriform plantar hyperplasia is nearly pathognomonic for PS [4]. However, isolated plantar collagenomas, limited forms of Proteus syndrome due to mosaic mutations and minimal forms of PS with only skin hypertrophy and macrodactyly have been described [4, 5].

Aim

The aim of this case report was to present and discuss the unexpected finding of redundant plantar skin folds in a female patient, likely having a minimal form of PS, systemic lupus erythematosus and plantar panniculitis.

Case presentation

A 46-year-old female patient presented for intermittent symmetric wrist and ankle arthritis, foot pain and discomfort. Her history included photosensitivity, bilateral ovarian cystadenoma diagnosed in her twenties, an anxious disorder for which she repeatedly refused a cerebral MRI (magnetic resonance imaging), and recurrent painful nodular swellings on the limbs and soles. A biopsy from an arm nodule performed four years prior to presentation had shown lobular and septal granulomatous panniculitis. Physical examination revealed a discrete malar rash, downslanting palpebral fissures with discrete right ptosis, bilateral redundant plantar skin folds (Figure 1a), a small cerebriform fibrotic hyperplasia on the left sole (Figure 1b), second and third syndactyly and a larger first right toe, noted since childhood. No other family member was affected.

The biopsy of the plantar cerebriform hyperplasia showed a plantar collagenoma, with hyperorthokeratosis, epidermal flattening, thickened collagen bundles, few fibroblasts and no elastic fibers (Figure 1c). A PS with minimal dysmorphism was therefore suspected. The biopsy from the plantar tegument clinically affected by panniculitis revealed parakeratosis, some dermal fibroplasia and edema, moderate lymphohistiocytic inflammatory infiltration with eosinophillic predominance, consistent with early erythema nodosum.

Laboratory tests showed mild inflammation [ESR (erythrocyte sedimentation rate) 23 mm/h, CRP (C-reactive protein) 8 mg/L – normal values <6 mg/L], leukopenia [3200 WBC (white blood cells)/μL] with lymphopenia (900/μL), thrombocytopenia [95 PLT (platelets)/μL] and positive antinuclear antibody (ANA) with a homogenous

and peripheral pattern (1/320), anti-dsDNA (double stranded DNA) antibodies (84 IU, normal values <20 IU), and anti-Ro antibodies (32 IU, normal values <20 IU). We also found no complement consumption, anticardiolipin IgG, anti-beta-2 glycoprotein IgG antibodies, lupus anticoagulant, rheumatoid factor, ANCA (anti-neutrophil cytoplasmic antibodies) p and c, anti-CCP (cyclic citrullinated peptides) antibodies, viral hepatitis tests [anti-HCV (hepatitis C virus) antibodies and HBs (hepatitis B surface) antigen] or anti-streptolysin O titer increase. Pharyngeal smear, urine culture, *Chlamydia pneumoniae*, *Mycoplasma hominis* and *Ureaplasma urealyticum* screening tests, interferon-γ release assay (quantiferon), calprotectin and fecal occult blood test were negative. Metabolic parameters (liver function tests, alkaline phosphatase, uric acid, glycemia) were normal, apart from low-density lipoprotein (LDL)-cholesterol (165 mg/dL, normal <100 mg/dL) and triglycerides (165 mg/dL, normal <150 mg/dL). High-density lipoprotein (HDL)-cholesterol, amylase, angiotensin convertase and alpha-1 antitrypsin were also within reference ranges. Hand radiograph showed juxtaepiphyseal osteoporosis, while chest radiograph was normal.

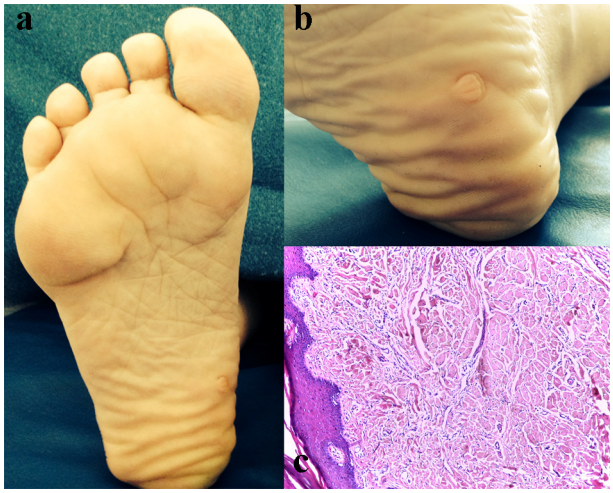

Figure 1 – ***(a) Redundant skin folds on the anterior sole; (b) Small plantar cerebriform hyperplasia; (c) Biopsy of plantar cerebriform hyperplasia: thickened collagen bundles, with rare fibroblasts, hyperorthokeratosis and epidermal flattening, suggesting a collagenoma (Hematoxylin–Eosin staining, ×100).***

Therefore, we formulated a diagnosis of systemic lupus erythematosus (SLE) and the recurrent panniculitis was interpreted as secondary, although the biopsy was not typical for lupus panniculitis. No pulmonary, cardiac or renal SLE-related involvement was present. The general screening (including abdominal ultrasonography, chest radiograph, mammography, genital examination with Pap smear, thyroid and ophthalmologic examinations) was negative for neoplasia as well.

She received low-dose Prednisone with tapering, Hydroxychloroquine, non-steroidal anti-inflammatory drugs and low-dose Aspirin, with marked improvement of her arthritis and foot pain and no further episodes of panniculitis.

Discussion

Redundant plantar folding is an uncommon finding in an adult. Increased plantar folding results from developmental or acquired connective tissue disorders, involving different plantar structures, mainly the adipose panniculus [6, 7]. Dysregulated adipose tissue (lipodystrophy or lipomatosis) and panniculitis may all contribute. The occurrence of SLE in a patient with a hamartomatous syndrome is very rare [8] and raises intriguing pathogenesis questions regarding the interplays between adipose tissue regulation pathways, inflammation and possibly morphogenesis [9–11].

Redundant plantar folding in the case presented was mainly due to *cutis laxa* (CL) describing loose, sagging skin with reduced elasticity, inherited or acquired, due to elastin defects [12]. Of interest, in acquired CL cultured fibroblasts show increased elastolytic activity, while in PS the collagenase expression in fibroblasts is reduced [12, 13]. The alpha-1 antitrypsin deficiency is involved in panniculitis, as well as in CL [14]; in our patient, however, its level was normal. Acquired CL (elastolysis) may accompany relapsing lobular non-suppurative panniculitis, evolving with episodic recurrent fever, rash and leukocytosis [12, 14]. The numerous etiologies include SLE, alpha-1 antitrypsin deficiency, trauma, etc. [2]. Lupus panniculitis or lupus profundus occurs in 2–3% of SLE cases, usually on the upper third of arms, cheeks and breasts, as infiltrating erythematous nodules leaving characteristic cup-shaped depression, not present in our case. Lupus panniculitis is a lobular panniculitis with broadened fibrotic septa and hyaline changes extending into the lobules, sometimes resembling a subcutaneous panniculitis-like T-cell-like lymphoma, but having vacuolar changes and dermal mucin deposition [2, 6]. The current panniculitis biopsy in our case was compatible to an erythema nodosum. Plantar lipoatrophy due to panniculitis has not been described in this setting, to the best of our knowledge. Lipoatrophy generally follows the areas of previous inflammation [15]. Intriguingly, in our patient the panniculitis was followed by atrophy only on the soles and not on the arms, possibly due to the standing pressure on the soles or other local factors [14].

Dysregulated adipose tissue, including regional lipohypoplasia, is described in PS, a very rare sporadic disorder causing postnatal overgrowth of multiple tissues in a mosaic pattern, due to AKT1 gene mutations [3]. The diagnosis of PS is based on clinical criteria, according to Biesecker & Sapp [3]. Our patient fulfilled the required criteria, having the general characteristics, the small plantar collagenoma (a major criterion), the toe overgrowth, downslanted palpebrae with minor ptosis and bilateral ovarian cystadenoma. The differential diagnosis in this case included the other Proteus-like syndromes with sole involvement, but associating vascular anomalies, CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal) and SOLAMEN (segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus) syndromes (Table 1). Gene sequencing was not possible in our patient.

This unusual association of plantar panniculitis and PS may give rise to some speculations. Inter-organ communication in developmental, metabolic and immune response processes is co-coordinated by peroxisome proliferator-activated receptors (PPARs) expressed on macrophages and adipocytes, of which PPARγ likely has a pivotal role

[16, 17]. As AKT1 and PTEN (phosphatase and tensin homolog) belong to the regulatory pathways of PPARγ, their mutations result in dysmorphogenesis and abnormal fat distribution [10, 11]. PPARγ expression induction requires AKT1, mutated in PS, while mutations of PI3K (phosphoinositide 3-kinase), an upstream AKT1 activator, are involved in the PS-like CLOVES syndrome [3, 17, 18]. Moreover, PPARγ upregulates PTEN. Germline PTEN mutations, correlated with lipomatosis, are found in 20% of PS and 50% of PS-like syndromes, including the SOLAMEN syndrome [10, 11]. PI3K, AKT and PTEN are key members of the PI3K/AKT/mTOR (mammalian target of rapamycin) intracellular cell-signaling pathway, involved in oncogenesis, insulin sensitivity and lipomatosis, and PI3K and mTOR are immune regulators in immune cells [19].

Table 1 – ***Inherited disorders with dysregulated adipose tissue on the extremities***

Disorder		Characteristics	Mutation	References
Hamartomatous disorders	Proteus syndrome	Segmental overgrowth, lipomatosis, connective tissue nevi.	AKT1	[3]
	SOLAMEN syndrome	Segmental overgrowth, lipomatosis, soft tissue hypertrophy with ballooning effect, arterio-venous and lymphatic malformations, linear epidermal nevi, macrocephaly, breast and thyroid hamartomas.	PTEN	[3, 10]
	BRRS	Macrocephaly, lipomatosis, intestinal polyposis, freckled penis.		
	CLOVES syndrome	Congenital lipomatous overgrowth, vascular anomalies and epidermal nevi, skeletal and spinal anomalies/scoliosis.	PIK3CA	[3, 18]
	FAO/HHML	Fibroadipose hyperplasia or overgrowth/hemihyperplasia multiple lipomatosis.		
	MCAP	Megalencephaly–capillary malformation.		
Lipodystrophies	Familial partial lipodystrophy (Dunnigan type)	Loss of subcutaneous fat, mainly from extremities, increased fat deposits on face and neck, dyslipidemia, hepatic steatosis, arterial hypertension, insulin resistance.	PPARγ LMNA	[14]

SOLAMEN: Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus; BRRS: Bannayan–Riley–Ruvalcaba syndrome; CLOVES: Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal; FAO/HHML: Fibroadipous overgrowth/hemi-hyperplasia/multiple lipomatosis; MCAP: Megalencephaly/capillary malformation; PTEN: Phosphatase and tensin homolog; PPARγ: Peroxisome proliferator-activated receptor γ; LMNA: Gene encoding nuclear lamins A and C.

PPARγ is increased in active SLE having anti-inflammatory effects [9]. Panniculitis responded to Hydroxychloroquine (HQ) in our patient. Besides the favorable metabolic effects, antimalarials have anti-oncogenic properties by modulating autophagy and by inhibiting mTORC1 (mammalian target of rapamycin complex 1), part of the AKT/mTORC intracellular signaling pathway [20]. It is therefore tempting to speculate that HQ could also be used in diseases involving dysregulated growth, like the hamartomatous syndromes.

Conclusions

Redundant plantar folds in our patient likely resulted from localized lipoatrophy. Inflammation in SLE and possibly pressure and adipose dysregulation in PS led to increased plantar folding. This case further illustrates the links between adipose tissue regulation, inflammation, lupus, and lipodystrophy. The diagnosis and treatment of an over imposed inflammation in PS could help limit the plantar damage.

Conflict of interests

The authors declare that they have no conflict of interests.

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Informed consent

Written informed consent was obtained from the patient for this case report and the accompanying images.

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Corresponding author
Siao-Pin Simon, Lecturer, MD, PhD, Department of Rheumatology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8 Victor Babeş Street, 400023 Cluj-Napoca, Romania; Phone +40745–665 119, Fax +40264–431 040, e-mail: siao_2003@yahoo.com

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