Redundant plantar skin folds

LAURA OTILIA DAMIAN1), SIAO-PIN SIMON2), IOANA FELEA1), CAROLINA BOTAR-JID3), BODGAN STANCU5), LILIANA ROGOJAN5), CRISTINA ANA MARIA PAMFIL2), ADRIANA ALBU6), SIMONA REDNIC2)

1) Department of Rheumatology, Emergency County Hospital, Cluj-Napoca, Romania
2) 2nd Department of Surgery, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
3) Department of Radiology, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
4) 2nd Department of Surgery, “Iuliu Hatieganu” 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 Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract
A 46-year-old female patient presented for intermittent symmetric wrist and ankle arthritis, episodic plantar pain and strikingly redundant plantar skin folds, likely due to lipatrophy 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 lipatrophy in this setting are discussed. This case enlightens 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 lipatrophy 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 hyperthokeratosis, 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 eosinophilic 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, antcardiolipin 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.

 agua}  

**Discussion**

Redundant plantar folding is an uncommon finding in an adult. Increased plantar folding results from develop-
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**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Characteristics</th>
<th>Mutation References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteus syndrome</td>
<td>Segmental overgrowth, lipomatosis, connective tissue nevi.</td>
<td>AKT1 [3]</td>
</tr>
<tr>
<td>SOLAMEN syndrome</td>
<td>Segmental overgrowth, lipomatosis, soft tissue hypertrophy with balloonning effect, arterio-venous and lymphatic malformations, linear epidermal nevi, macrocephaly, breast and thyroid hamartomas.</td>
<td>PTEN [3, 10]</td>
</tr>
<tr>
<td>BRRS</td>
<td>Macrophagy, lipomatosis, intestinal polyposis, freckled penis.</td>
<td></td>
</tr>
<tr>
<td>CLOVES syndrome</td>
<td>Congenital lipomatous overgrowth, vascular anomalies and epidermal nevi, skeletal and spinal anomalies/scoliosis.</td>
<td></td>
</tr>
<tr>
<td>FAO/HHML</td>
<td>Fibroadipous hyperplasia or overgrowth/hemi-hyperplasia multiple lipomatosis.</td>
<td>PIK3CA [3, 18]</td>
</tr>
<tr>
<td>MCAP</td>
<td>Megalencephaly–capillary malformation.</td>
<td></td>
</tr>
</tbody>
</table>


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 antioncogenic 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**

Reducant 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.

Acknowledgments

The authors want to gratefully acknowledge the contribution of Associate Professor Dr. Ioan Parasca, their mentor. Funding: PN-II-RU-TE-2014-4-2708.

Informed consent

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

References


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

Received: October 20, 2015
Accepted: November 10, 2016