Title: **Generalized scleroderma-like induration associated to D-penicillamine *elastosis perforans serpiginosa* in Wilson's disease**

Running Head: ***Generalized scleroderma-like induration***

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Wilson's disease is a rare autosomal recessive neurometabolic disorder of copper metabolism, whose treatment consists of metal ion excretion with the use of copper chelating agents, among which D-penicillamine is used most frequently. Skin adverse effects of long-term administration of D-penicillamine are usually associated with the local occurrence of *elastosis perforans serpiginosa*.

We present a devastating case, occurred in a 42-year-old woman, whose skin was beyond the typical figurate papular and keratotic lesions, as a whole apparently not affected skin was indurated, with a generalized 'cardboard' consistency reminiscent of scleroderma and/or scleromyxedema, simulating the "sharpei sign" on trunk. This peculiar presentation was significantly different than other previous skin changes associated to D-penicillamine administration.

A 42-year-old woman, affected by *Wilson's disease* (WD), and on treatment with *D-penicillamine* (DPA) from the age of 7, was referred to our clinic for the occurrence of chronic abscesses on axillary, inguinal and genital regions, in the suspicious of *hidradenitis suppurativa* (chronic, recurrent, and debilitating skin condition, due to an inflammatory disorder of the follicular unit and associated with multiple comorbidities[1]). Physical examination confirmed the presence of some aching nodules and purulent abscesses on armpits and groins, but surrounded and contiguous to multiple annularly and serpiginously arranged small brownish keratinized papules (Figure 1A), present also on the neck and upper back (Figure S1).

The patient never suffered of other D-penicillamine side effects, including dysgeusia, gastrointestinal, renal, hematological disorders or myasthenic syndrome. As regard WD, the patient was asymptomatic and follow-up was performed twice a year by the hepatologist and neurologist, with complete blood and urine routine tests, serum copper and ceruloplasmin dosage. Additional instrumental examinations were performed annually.

<Figure 1>

Papular lesions were asymptomatic, and the patient had not given them relevance until the appearance of inflammation, and purulent discharge. However, the general appearance of the skin was peculiar, beyond the evident inflammatory lesions, fixed and hard in consistency, with exaggerated accentuation of the normal wrinkles, not pliable, and completely inelastic (Figure 1E; Figure S1). This abnormal induration was reminiscent of *sclerodema* and/or the peculiar alterations described in *scleromyxedema* as "sharpei sign".

<Figure 2>

Diagnostic work-up included three skin biopsies from: **(1)** an inflammatory nodule of the right armpit, **(2)** keratinized papules of the back; and **(3)** the apparently healthy, but indurated skin of the back. Histopathological findings were consistent with *elastosis perforans serpiginosa* (EPS) on all specimens (Figures 1-2), even on the hidradenitis suppurativa-like nodule **(1)**, where the accentuated inflammatory presentation was justified by a deep dermal mixed inflammatory infiltrate (Figure 1). Abundant multinucleated giant cells, phagocytizing an eosinophilic material, were further identified by histochemistry as elastic fibers (Figure 1). The biopsy on apparently not affected skin **(3)** showed diffused dermal damage, with thickened, fragmented, and intertwined bundles (Figure 1E-H), identified as elastic fibers on specific stains (Figure 2E and 3F). Thus,

scleroderma like disorders were excluded[2], and the indurated skin candidates as a new exaggerate presentation of the dermal damage, in the spectrum of DPA-EPS abnormalities.

Literature retrieval to find previous description of such widespread indurated skin alteration addressed the differential diagnosis with other known DPA-induced dermal damages[3-12], which could be expressed concomitantly in our patient.

Anetoderma (*macular atrophy*) was excluded in our patient, while it consists in well-circumscribed, roundish, skin-colored or white, atrophic macules or patches of wrinkled skin[13]. *Cutis laxa* was also discarded, while it is clinically characterized by loose, not indurated redundant skin, which histopathology shows elastolysis-in opposition to elastosis, with reduced and fragmented dermal elastic fibers[14]. A DPA-induced *pseudoxanthomas elasticum* (PXE)[11] was suspected. Nevertheless, the texture of the skin should be more irregularly pebbled, described as 'plucked-chicken' skin. The most important histological feature of PXE is *mid dermis elastorrhexis*, with progressive fragmentation and mineralization of the elastic fibers. The negative Goldner staining in our specimen further excluded elastic fiber's calcification, which is a very pathognomonic finding in PXE.

No signs of DPA-related skin fragility over bony prominences and pressure area, nor *ecchymosis*, *milia* and *lymphangiectasia* were observed in our patient.

Among DPA-induced disorders of connective tissue, EPS is the best characterized[6-9]. Our observation widens the spectrum of clinical presentation of EPS, ranging from very inflammatory involvement of the groins, so severe to mimic *hidradenitis suppurativa* to an indurated scleroderma-like alteration of the skin not apparently affected with the typical papule-keratotic annular EPS lesions. Histopathology[15] was crucial to document superimposable EPS findings in all skin biopsy, excluding other potentially DPA-associated conditions.

Skin changes improvement is described with DPA withdrawal or consistent dose reduction[3], thus DPA therapy was dismissed and replace with oral trientine hydrochloride indicated in WD therapy[3].

After one-year-follow-up true EPS isolated lesions greatly improved, but only slight softening of skin on trunk and proximal limbs, with some increased flexibility of movements. A possible explanation of such severe and widespread elastic tissue damage in our patient is consistent with the very young age, 7 year-old, at which the DPA treatment was introduced.

The presented here peculiar "scleroderma-like" skin alteration in a patient with DPA-induced EPS has not been previously described in the literature. Histology was different than other DPA-induced

dermopathy: similar to EPS, with thickened elastic bundles, fragmented and tangled, but without trans-epidermal elimination. It is likely that metal-chelation therapy[16] with DPA since childhood has induced an extensive dermal damage, with a dense and knotted organization of the abnormal elastic bundles in the whole skin, giving a peculiar cardboard appearance.

The precise amount of DPA required to produce elastic fibers damage is unknown, but it has been estimated that a minimum of 1 g daily for more than 5 years is necessary to induce visible changes. The presented here case study warns against DPA-administration in young age, when connective tissues are under development, to avoid generalized and not-reversible skin changes. Dermatologist has an important role in the follow-up of the patients treated with DPA, because cutaneous damage could be a clear signal of inappropriate dosage of the drug. Early recognition of penicillamine-induced skin changes is important since these abnormalities may not be restricted only to the skin, but may be markers of more widespread, multi-systemic involvement.

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