PRURIGO NODULARIS ASSOCIATED WITH AUTOIMMUNE POLYENDOCRINOPATHY

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Summary

Introduction: *Prurigo nodularis (PN) is a dermatosis of unknown etiology, characterized by extremely pruritic papules and nodules symmetrically located on the extensor sides of the limbs and sometimes on the trunk. The etiology of PN has been associated with thyroid diseases, diabetes, chronic renal failure, cholestatic autoimmune hepatitis, internal neoplasia, HIV and HCV infection and psychiatric disorders. We present the case of a female patient with PN associated with autoimmune polyendocrinopathy.*

Clinical case: *A 43 years old female patient known with PN for about 10 years, with type 1 insulin-dependent diabetes mellitus complicated with stage 3 chronic kidney disease, with Basedow-Graves disease since 2014, is admitted into our clinic in October 2017 with the following accuses: progressively altering neuromuscular asthenia, gastrointestinal disturbances, progressive hyperpigmentation of the skin, intensely pruritic, hyperpigmented nodules symmetrically disseminated on the trunk, limbs and face. Corroborating clinical and laboratory data, the diagnosis of Addison's disease in the context of autoimmune polyendocrinopathy was established. Histopathological examination of a skin nodule indicated the diagnosis of PN. For the skin disorder, 200 mg dapsone therapy was indicated, gradual disappearance of nodules and pruritus has been observed, residually remaining small atrophic and achromic scars.*

Conclusions: *The particularity of this case is the association of nodular prurigo with three autoimmune diseases during an autoimmune polyendocrinopathy: type 1 insulin-dependent diabetes mellitus, Graves' disease and Addison disease.*

Key words*: prurigo nodularis, autoimmune polyendocrinopathy, Graves' disease, Addison disease, diabetes mellitus.*

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Introductions

Prurigo nodularis (PN) is a dermatosis of unknown etiology characterized by extremely pruritic nodules with well-defined clinical and histopathological aspects.[1] PN is characterized by numerous, persistent, intensely pruritic erupting on the extensor sides of the limbs occurring mainly in adults, especially middle-aged women.[2] Once PN have occurred, complete resolution of lesions is uncommon. Pruritus and progressive extension of involved area deeply affect the lives of the patients affecting everyday activities and sleep. The etiology of PN has been associated with thyroid diseases, diabetes, chronic renal failure, cholestatic autoimmune hepatitis, internal neoplasia, HIV and HCV infection and psychiatric disorders. [3, 4] We present the case of a female patient with PN associated with autoimmune polyendocrinopathy.

Clinical case

A 43 year old female patient diagnosed with PN for about 10 years, with type 1 insulin-dependent diabetes mellitus complicated with stage 3 chronic kidney disease since 2010 and

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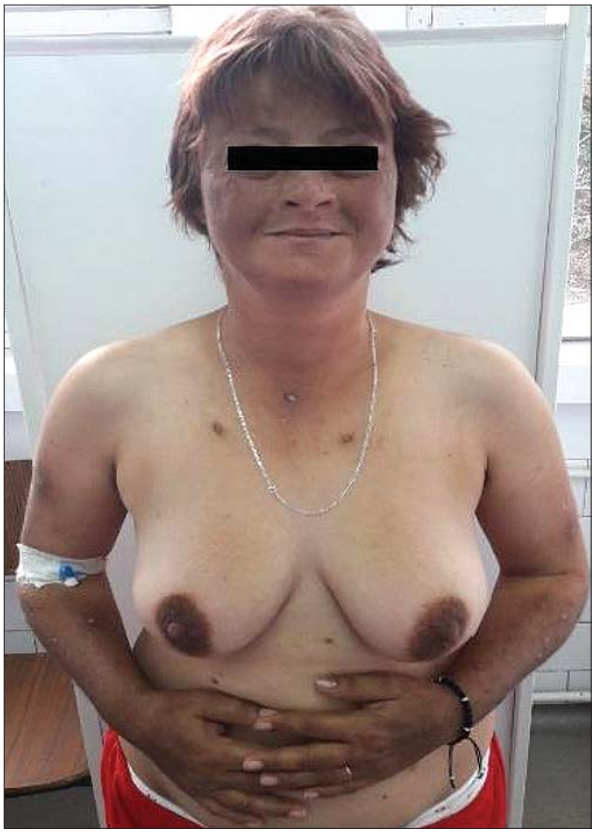
Basedow-Graves' disease with antithyroid medication since 2014, mixed anxiety-depressive disorder, was admitted in our clinic in October 2017 presenting progressive cutaneous hyperpigmentation, intensely pruritic, excoriated, hyperpigmented nodules symmetrically disseminated on the limbs, trunk and face. Anamnesis showed no history of trauma or insect bites.

General examination showed an afebrile patient with mediocre general status, progressive worsening asthenia, bilateral exophthalmia, gastrointestinal disturbances (nausea and repeated vomiting), progressive weight loss, poor adipose tissue, paresthesia of the limbs, bradycardia (48 times a minute) and blood pressure 80/50 mm Hg. The patient also presents amenorrhea for 5 months with negative pregnancy test.

Dermatological examination revealed dry skin with low elasticity, with numerous intensely pruritic, excoriated, hyperpigmented nodules with a diameter of about 1 cm, presenting a crust in the center. The nodules were disseminated across the lower and upper limbs, trunk and face. The nodular lesions had an evolution of about 10 years, with the continuous development of new lesions while the older lesions regressed spontaneously or under therapy. An intense progressive hyperpigmentation of the face, palmar and greater folds started 6 months ago (fig. 1, 2 and 3). In our case, differential diagnosis should be made with generalized eruptive keratoacanthomas, nodular pemphigoid, verrucous tuberculosis, cutaneous lymphomas, hypertrophic lichen planus and nodular scabies.

Histopathological examination of a cutaneous nodule described important acanthosis with uneven elongation of interpapillary ridges, hyperkeratosis with parakeratosis and hypergranulosis. In the center of the lesion the epidermis was ulcerated by the presence of a fibrino-leukocytic exudate. Papillary dermis presented extensive fibrosis with vertically



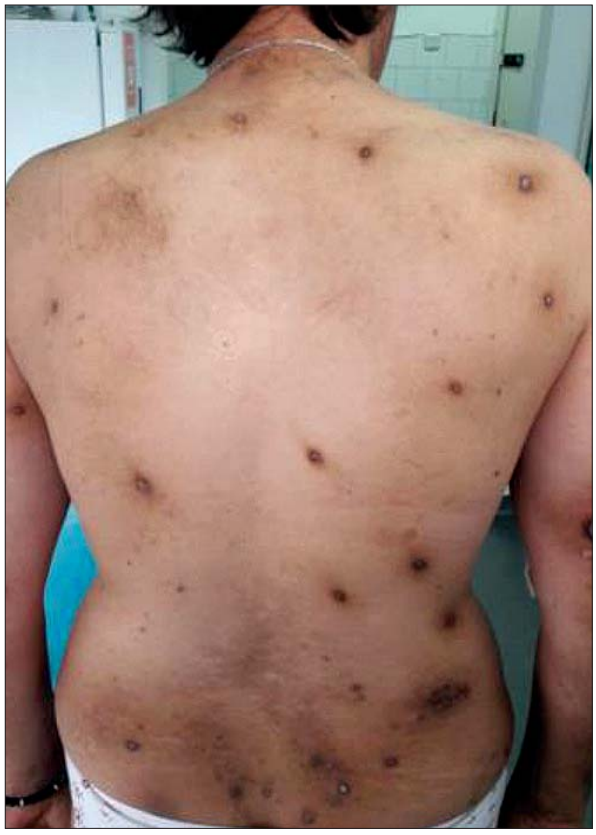


Figure 1 – Intense hyperpigmentation of the face, hands and forearms

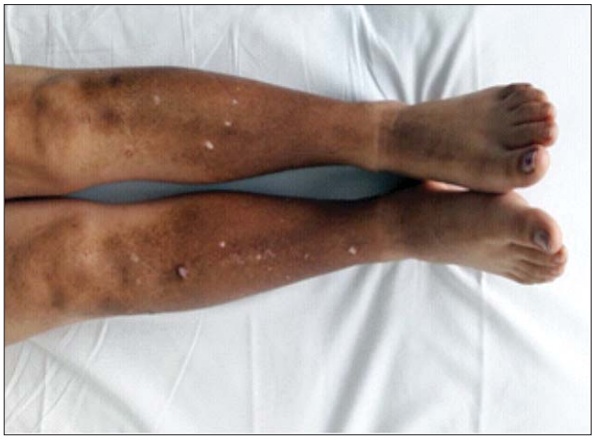


Figure 3 – Excoriated nodules on hyperpigmented skin of extensor side of the calves

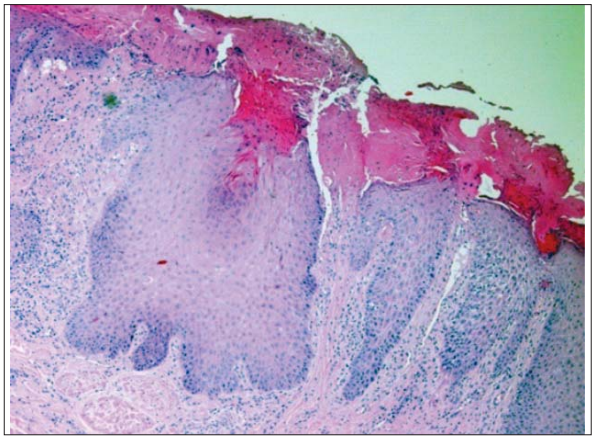


Figure 4 – Prurigo nodularis – histopathological appearance (hematoxylin and eosin stain)

oriented collagen bands. Deep dermis showed a discreet chronic perivascular lymphocytic infiltrate (fig. 4). Histopathological examination stated the diagnosis of prurigo nodularis.

Laboratory investigations showed eosinophilia (6.8%), hyponatremia, hyperkalemia, increased values of glycaemia, glycosylate hemoglobin, urea and creatinine, increased antithyreoperoxidase antibodies, ACTH, and low basal and ACTH stimulated cortisol. Viral markers for hepatitis B and C and HIV test were negative (Table I).

Chest X-ray, abdominal ultrasonography, and cerebral MRI have showed no pathological signs. Thyroid gland echography showed a homogenous structure with no nodular of cystic lesions, and parathyroid glands with increased diameters, homogenous globular structure, with lower echogenity in comparison to the thyroid parenchyma. Abdominal CT scan showed atrophic suprarenal glands.

Corroborating clinical and laboratory data, the diagnosis of primary adrenal insufficiency (Addison disease) in the context of an autoimmune polyendocrinopathy (type 1 diabetes mellitus and Graves' disease) was established.

Volumetric and hydroelectrolytic rebalancing therapy and substitution therapy with prednisone 7.5 mg/day and fludrocortisone 0.1 mg/day was performed. Since the diagnosis of nodular prurigo was made, the patient has repeatedly been receiving H1 antihistamine therapy, potent topical corticosteroids, cryotherapy, but with unsatisfactory and short-term results. A therapy with dapsone 200 mg/day has been recommended from November 2017. Under this therapy evolution was favorable with the gradual disappearance of nodules and pruritus, leaving small atrophic and achromic scars.

Table I – Laboratory investigations

Laboratory investigations (unit)	Patient values	Laboratory reference values
Haemoglobin (g/dL)	12	11.7-15.5
Hematocrit (%)	34.3	35-45
Leukocytes (103/uL)	5.42	4-10
Platelets (103/uL)	248	150-450
Glycaemia (mg/dL)	144.46	75-105
Hb A1c (%)	7.7	4.8-5.6
Urea (mg/dL)	50.9	10-50
Creatinine (mg/dL)	1.45	0.5-1.2
Seric sodium(mmol/L)	130	136-145
Seric potassium (mmol/L)	6.84	3.5-5.1
FT4 (pmol/L)	11,6	12-22
TSH (uIU/mL)	5.09	0.27-4.5
Antithyroglobulin antibodies (U/mL)	0,2	0-100
Anti-thyroid peroxidase antibodies (IU/mL)	801.68	0-50
Estradiole (pg/mL)	31	<28
Testosterone (ng/mL)	0.23	0.14-0.76
FSH (UI/L)	54.07	23-116.30
Basal cortisol (nmol/L)	58.94	64-536
Cortisol - ACTH stimulation test (nmol/L)	61.23	64-536
ACTH (pmol/L)	1354	1.6-13.9
G-6-PD (U/gHb)	9.8	8.0-13.0

Discussions

PN is characterized by numerous intensely pruritic, brown nodules of approximatively 1 cm in diameter, with a hyperkeratotic surface and excoriations covered by crusts due to the intense scratching, symmetrically disseminated especially on the extension sides of the limbs and trunk.[5] On the posterior thorax there may be an area without skin lesions due to the patient's inability to scratch, called the "butterfly sign". [6, 7]

Skin inflammation and neural plasticity appear to play an important role in PN, but the exact pathogenicity of the condition remains unclear. [6] Chronic scratching of the skin causes nodular lichenification, hyperkeratosis and hyperpigmentation. On a scale of 1 to 10, the intensity of pruritus within the PN is at level 8. Most patients say pruritus is not just a simple skin sensation, but a combination of stuttering, burning, tingling, cold and hot, regardless of the etiology of PN.[3] Chronic scratching may be the major trigger of PN. Because of the neuronal sensitivity to pruritus, a vicious pruritus-scratching circle is formed, which ultimately leads to a decrease in quality of life, including sleep disturbances and psychiatric disorders. [8, 9, 10]

Histopathological examination of PN reveals an increase in intradermal nerve fiber density, altered mast cells, collagen fibers, Merkel cells, epidermal keratinocytes, dendritic cells and endothelial cells. [11] These cells cause inflammation and pruritus by the release of IL-31, prostaglandins (PG), histamine, triptaze, neuropeptides and nerve growth factor (NGF). Increasing the level of NGF makes substance P (neuropeptide that transmits pain to CNS) to induce a signal that contributes to dermal and neural hyperplasia. [12] Sensory nerve hypoplasia was detected in the epidermis of patients with PN compared to that of healthy patients, suggesting the presence of a subclinical small fiber neuropathy in prurigo nodularis. Pereira et al.[13] suggested that scratching may be the cause of the reduced intradermal nerve fiber density and not an underlying neuropathy. Repeated biopsies from the nodular lesions of PN undergoing healing have shown a repair of the density of sensitive nerve fibers, which supports the theory that the disturbed epidermal anatomy is secondary to the mechanical trauma rather than a functional neuropathy. [14]

PN association with thyroid disorders, diabetes mellitus,[15] chronic renal failure (18-60%),[16] autoimmune hepatitis hepatitis, neurological diseases,[17] internal neoplasia, HCV infection, HIV infection [18] and psychiatric disorders [19] are cited in the literature. PN was also identified in 50% in patients with atopy. [20] Although autoimmune disorders are not classically associated with PN, there is evidence that it may involve TH1 and TH2 cytokines. In one study, 19 of 22 patients with PN had immunostaining with anti-pSTAT-6 throughout the epidermis.[21] Anti-pSTAT-6 is a marker for the TH2 cytokines interleukin IL-4, IL-5 and IL-13. In addition, 8 patients had dispersed staining with anti-pSTAT-1, a marker for the TH1 cytokines interferon γ and IL-27. On the basis of these patterns, TH1 and TH2 cytokines may participate in the pathogenesis of PN. [13, 21]

The therapy in PN consists of topical corticoids, capsaicin, calcineurin inhibitors, UV therapy, and systemic gabapentin, opioid receptor antagonists, anti-depressives and immunosuppressors. The latest therapeutic concept consists of the administration of inhibitors of neurokinin A and IL-31 receptors, which are currently in the clinical trial phase. [22] Neurokinin A, also known as substance K, is a neurological active peptide, with excitatory effects on the nervous system, which influences the inflammatory response and pain reception. Interleukin-31 is a proinflammatory cytokine that influences immune mediation, identified in most chronic inflammatory diseases. Studies done on mice show that IL-31 derivate from T-Cells induce severe pruritus and inflammation due to the connection to a IL-31 receptor. [23] Due to the lack of response to antihistamines, it is highly probable that histamine is not a major mediator in PN.[24] We have presented the case of a female patients with PN with a chronic evolution of

about 10 years, marked with repeated bursts, reluctant to antihistaminic therapy, potent topical corticoids and cryotherapy. The therapy that registered a success was Dapsone 200 mg/day for 2 months than 100 mg/day with gradual disappearance of nodules and pruritus, with small hypopigmented atrophic residual scars.

ConclusionS

The particularity of the case presented is the association of PN with three different auto-immune condition in the context of an auto-immune polyendocrinopathy: Graves` disease, type 1 diabetes mellitus and Addison disease.

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Conflict of interest
NONE DECLARED

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