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Clinical Case Seminar

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Urticaria and hyposideremia: a case report

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Abstract

The authors report the case of an 86-year-old man with a six-month history of chronic idiopathic urticaria, refractory to standard treatments. The patient did not report concomitant diseases and all clinical tests performed were normal. Laboratory tests showed only mild anemia and low serum iron (31 mcg/dl, normal value 59-158). After oral iron supplementation (105 mg/day of elemental iron, taken as ferrous sulphate) for two months, normal serum iron levels and complete remission of urticaria were observed. No further episodes of urticaria were reported at follow-up visits, six and twelve months later.

The possible link between hyposideremia and urticaria is also discussed. *In vitro* experimental data suggest that transferrin inhibits histamine release from mast cells, and a direct correlation exists between the level of transferrin saturation and the degree of inhibition of histamine release. Reduced transferrin saturation due to hyposideremia could lower the threshold of stimulation required for mast cell degranulation, thus increasing the risk of urticaria in response to endogenous and/or exogenous pathogenic stimuli, even minimal. Further studies are necessary to better understand frequency and pathogenic mechanism(s) of "sideropenic urticaria" (chronic urticaria associated with hyposideremia and favourably responding to iron supplementation). From a clinical point of view, evaluation of serum iron levels in selected patients appears advisable, in the light of the relatively low cost and possible significant benefits

Key-Words: chronic urticaria, hyposideremia, etiopathogenesis, iron supplementation, therapy.

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Introduction

Chronic urticaria (CU) affects about 1% of the general population, and its clinical manifestations, particularly intense itch, can severely interfere with daily activities and/or sleep. Identification of cause(s) and treatment of CU can be challenging tasks for clinicians, because the etiopathogenic mechanisms of the disease are multiple and not yet completely clear, and antihistamines and/or corticosteroids are sometimes insufficient to induce complete remission [1].

Case report

An 86-year-old man came to our observation with a six-month history of multiple erythematous-purplish lesions, mainly located on the trunk (**Figure 1**).

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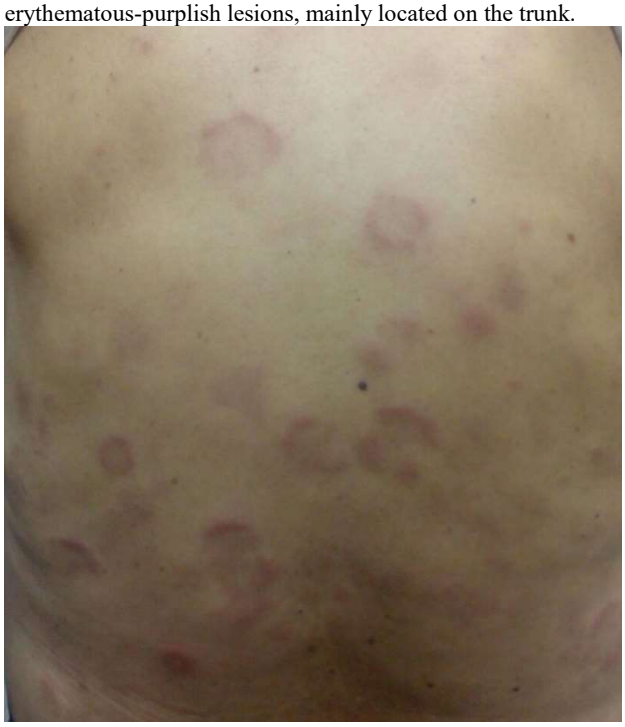
Figure 1. Clinical picture of the patient: multiple erythematous-purplish lesions, mainly located on the trunk.



These lesions were circular or arc-shaped, not confluent, infiltrative and palpable, intensely itching, and were refractory to systemic therapy with antihistamines and corticosteroids.

Medical history of the patient was negative for significant diseases. Previous skin prick tests with aeroallergens and food allergens, patch tests with the standard series of haptens recommended by SIDAPA (Società Italiana di Dermatologia Allergologica, Professionale e Ambientale – Italian Society for Allergological, Occupational and Environmental Dermatology), search for *Helicobacter pylori* and search for parasites and occult blood on three stool specimens had yielded negative results. Other laboratory tests, performed two weeks before our visit, are shown in **Table 1** and **2**. Only signs of mild anemia were found, with a serum iron level of 31 mcg/dl (normal value 59-158 mcg/dl).

Our clinical suspicion was confirmed by histopathological examination of a specimen of lesional skin, obtained by punch biopsy, which showed no significant epidermal alterations and inflammatory infiltrate of lymphocytes, neutrophils and rather numerous eosinophils around superficial and deep dermal vessels.

Based on our previous clinical experience [1], oral iron supplementation (105 mg/day of elemental iron, taken as ferrous sulphate) for two months was suggested in addition to antihistamines.

Table 1. Results of the blood tests performed (values out of normal range are typed in boldface).

Test (unit of measure)	Value found	Normal range
Red blood cells (number x10^6/μL)	**4.04**	4.50-5.90
Hemoglobin (g/dL)	**12.6**	13-17
Hematocrit (%)	**38**	39-50
MCV (fL)	**81.7**	82-96
MHC (pg)	**26.8**	27-32
MCHC (g/dL)	**31.3**	32-36
RDW (%)	14.5	11.5-15.5
White blood cells (number x10^3/μL)	9.10	4-10
Neutrophils (number x10^3/μL)	7.29	1.80-7.50
Lymphocytes (number x10^3/μL)	1.22	1.20-4
Monocytes (number x10^3/μL)	0.53	0-0.80
Eosinophils (number x10^3/μL)	0.03	0-0.50
Basophils (number x10^3/μL)	0.03	0-15

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Platelets (number x10^3/μL)	200	140-400
Erythrosedimentation rate (mm/hour)	9	1-15
Total serum proteins (g/dL)	6.3	6.3-8.3
Albumin (% of total serum proteins)	55.8	55.8-66.1
Alpha 1 globulins (% of total serum proteins)	4.8	2.9-4.9
Alfa 2 globulins (% of total serum proteins)	10.1	7.1-11.8
Beta 1 globulins (% of total serum proteins)	5.5	4.7-7.2
Beta 2 globulins (% of total serum proteins)	4.7	3.2-6.5
Gamma globulins (% of total serum proteins)	17.8	11.1-18.8
Albumin/globulin ratio	1.21	1.10-2.40
IgA (g/L)	1.75	0.40-4
IgG (g/L)	11.93	7-16
IgM (g/L)	1.07	0.40-2.30
PT ratio (%)	109 %	70-120
INR	1	0.80-1.20
aPTT (seconds)	28	22-35
Fibrinogen (mg/dL)	355	150-450
Glucose (mg/dL)	107	60-110
Blood urea nitrogen (mg/dL)	34	10-50
Serum creatinine (mg/dL)	1.01	0.60-1.20
Uric acid (mg/dL)	5.7	3.5-7.2
Triglycerides (mg/dL)	62	40-170
Serum iron (μg/dL)	**31**	59-158
Transferrin (mg/dL)	301	200-400
Ferritin (ng/mL)	21.6	18-370
Na (mmol/L)	141	135-146
K (mEq/L)	4.5	3.5-5.3
AST (U/L)	22	0-42
ALT (U/L)	24	0-50
γGT (U/L)	26	0-50
C3 (mg/dL)	142	82-185
C4 (mg/dL)	35	15-53
C1-INH (mg/dL)	28	15-35
anti-streptolysin O (IU)	54	< 200
C reactive protein (mg/dL)	0.13	0-0.50
FT3 (pg/mL)	3.18	2.20-4.20
FT4 (pmol/L)	12	9-16
TSH (μIU/mL)	2.334	0.300-4.200
AbTg (IU/mL)	49	< 116
AbTPO (IU/mL)	2	< 9

After this period, the patient reported complete resolution of the cutaneous clinical picture, and serum iron levels were within the lower limits of normal (63 mcg/dl). As per our usual protocol [1], iron supplementation was suggested for another month, at the same daily dose. At follow-up visits after six and twelve months, progressive increase of serum iron (79 and 90 mcg/dl, respectively) was observed, and no relapses of urticaria were reported.

Table 2. Results of urinalysis.

Parameter (unit of measure)	Value found	Normal range
pH	6.4	5-8
specific gravity	1015	1001-1030
glucose (mg/dL)	0	< 130
proteins (mg/dL)	0	< 15
urobilinogen (IU)	0	0.2-1
red blood cells (number per high power field)	0	< 3

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white blood cells (number per high power field)	0	< 6
squamous epithelial cells (number per high power field)	5	< 20
bilirubin, ketones, nitrites, casts, crystals, bacteria, yeasts	not present	not present

Discussion

The most recent data available [2] suggest that the prevalence of chronic idiopathic urticaria in the Italian population is about 0.38%, and 23.09% of patients are aged 65 years or more. Recent Italian data about hyposideremia are lacking, but this condition is usually reported as common in elderly subjects [3]. Despite this, surprisingly few studies exist on the association between hyposideremia and CU. The first paper on this topic, dating back to 1975, reported hyposideremia in 22 of 77 patients with CU, some of which had improvements or complete remission after iron supplementation [4]. Many years later, Sharma [5] published a case series of five patients with mild-to-moderate iron deficiency anemia and CU due to nickel sensitivity. In three of these patients, treatment with low nickel diet and 150 mg/day of iron led to remission of urticaria in 3 to 4 weeks [5]. In 2014, we presented a study on 122 patients with chronic idiopathic urticaria (CIU) refractory to standard treatments [1]. Among those patients, about two thirds (n=81) had moderate hyposideremia. After adequate iron supplementation for 30 to 45 days, which led to restoration of normal serum iron levels, 64 of the above 81 reported complete remission of cutaneous manifestations and 17 an improvement superior to 80% in comparison to their basal disease severity score [1]. Association between hyposideremia and CIU, although with a lower frequency (16 of 188 patients), was then confirmed in another study [6]. The most recent version of the guidelines of the British Society for Allergy and Clinical Immunology for the management of chronic urticaria and angioedema reports that “if clinically indicated, measurement of serum iron and vitamin B12 levels can be useful” in the diagnostic workup of urticaria [7].

The new case presented here adds to the scarce number of reports in literature and confirms our previous results [1]. Another peculiarity of this case is the clinical resolution of urticaria with serum iron levels in the lower range of normal, an event observed in 3 of 15 similar cases in our previous experience [1] and not reported by other authors.

The pathogenic mechanism which links hyposideremia to CIU is still unclear, also because this condition is the result of a complex interplay of multiple individual and environmental factors. Rather old but interesting studies [8-10] demonstrated that transferrin is able to inhibit histamine release from mast cells, and a direct correlation exists between the degree of transferrin saturation and the degree of inhibition of histamine release. Hyposideremia reduces transferrin saturation, thus possibly lowering the threshold of stimulation needed for mast cell degranulation and, consequently, urticaria [1]. However, hyposideremia is not always associated with urticaria, because the onset of clinical manifestations also

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depends at least on the relative importance of the inhibitory effect of transferrin in mast cell homeostasis, the individual level of mast cell stability, and the type and magnitude of internal and/or external stimuli.

Conclusions

Further studies, on larger populations of different geographical and ethnic origin, appear desirable to better define frequency and importance of chronic urticaria associated with hyposideremia and favourably responding to iron supplementation (or, in our proposed definition, "sideropenic urticaria" [1]). Additionally, we believe that *in vitro* studies should be performed to understand the molecular mechanism(s) behind such association.

From a clinical point of view, available data suggest that evaluation of serum iron levels can be considered in the diagnostic workup of chronic and apparently idiopathic urticaria in selected patients, in consideration of the relatively low cost and possible significant benefits.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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