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# Chronic urticaria versus dermatomyositis in a case of T- cell large granular lymphocytic leukemia

**Floria Bertolini MD[1*], Luigi Clauser, MD[2]**

[1]Rovigo City Hospital-Dermatological Clinic Via G. Falcone, P. Borsellino, 69 45100 Rovigo, Italy.
[2]Istituto Stomatologico Italiano, Via Pace, 21-20122 Milano, Italy.

## ABSTRACT

**Aim:** The reported case involved a complicated diagnostic path, not only because of the usual difficulties specific to chronic urticaria but, also because the trigger was a T-cell large granular lymphocytic leukemia (T-LGLL), a rare type of leukemia with an indolent course whose etiology is still not well known. This leukemia is also known for its propensity to cause autoimmune diseases.
The aim of this study was to identify whether the muscle damage was caused by dermatomyositis or by T-LGLL.

**Methods:** After elevated muscle enzyme levels had been discovered magnetic resonance imaging (MRI) revealed muscle damage. Consequently, a muscle biopsy was performed in a targeted manner. In addition to muscle biopsy, transmission electron microscopy and anti-CN1A antibody testing were performed.

**Results:** MRI of the lower limbs and pelvic girdle indicated moderate fibroadipose substitution in many muscles, moderate edema in others. No involvement of the shoulder girdle and upper limbs.
Histological examination of the muscle fibers showed an “inflammatory myopathy with isolated phagocytotic fibers.” Inclusion-body myositis, which is known to be associated with chronic T-LGLL was excluded. On the same biopsy transmission electron microscopy confirmed inflammatory myopathy and anti-CN1A antibodies were positive. DNA extracted from the muscle of the micro-rearrangement for the y-chain of the TCR identified on the DNA extracted from peripheral blood was positive.

**Conclusions:** Conclusions: Chronic urticaria was an indication of immunoproliferative disease. Myositis was the pathology due to T-LGLL, and dermatomyositis was excluded.

**Keywords:** Chronic urticaria, myositis, immunoproliferative disease, T- cell large granular lymphocytic leukemia, muscular biopsy

***Correspondence to Author:**
Floria Bertolini, MD
Rovigo City Hospital-Dermatological Clinic Via G. Falcone, P. Borsellino, 69 45100 Rovigo, Italy.

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## Introduction

Chronic urticaria is often associated to the onset of neoplasms and especially to oncological hemopathy. For this reason, after the appearance of chronic urticaria, the research had the aim of exploring this association. The first findings were a gallbladder stone and a small monoclonal T population by molecular analysis for lymphoproliferative diseases, to be revealed at a later stage.

After cholecystectomy the patient referred almost complete regression of urticaria.

## Materials and Methods

A 55-year-old woman suffered from symptoms compatible with chronic urticaria.

Tests to identify the etiopathogenesis of urticaria a gallbladder stone and a small monoclonal T cell population was found by molecular analysis for lymphoproliferative diseases. The hematologist recommended annual checkups.

After cholecystectomy the patient had regression of urticaria. After one year, she repeated molecular analyses for lymphoproliferative diseases: there were no changes compared to the previous year.

**Table 1 ANALYSIS OF IMMUNOLOGICAL MARKERS IN FLOW CYTOMETRY ON PERIPHERAL BLOOD**

**White blood cell data when the atypical lymphocyte clone was identified**

| ***Test*** | ***Result*** | ***Reference values in peripheral blood*** |
|---|---|---|
| **VBC (x 10^9/L):** | 5.4 | |
| **%** lymphocytes | 55 | |
| Gate | lymphocyte | |
| area analyzed | 48% of total cells | |
| CD3 | 78 | (75% + 7) |
| CD5 | 76 | (75% + 7) |
| CD4 | 55 | (47% + 7) |
| CD8 | 29 | (30% + 6) |
| CD4+ CD8+ | 2 | (<5%) |
| Ratio CD4/CD8 | 1.9 | (1.7% + 0.6) |
| HLA-DR | 6 | (13% + 5) |
| CD8+ HLA-DR+ | 1 | (<5%) |
| CD3+ gammadelta+ | 7 | (4% + 3) |
| CD16 | 21 | (13% + 5) |
| CD56 | 24 | (13% + 5) |
| CD57 | 31 | (15% + 4) |
| CD3+ CD16+ | 7 | (<5%) |
| CD3+ CD56+ | 9 | (<5%) |
| CD3+ CD57+ | 18 | (6% + 3) |
| CD3- CD16+ CD56+ | 14 | (13% + 5) |
| CD3- CD16+ CD57+ | 13 | (<5%) |
| CD56+ CD57+ | 20 | (<5%) |
| CD19 | 5 | (10% + 3) |
| CD19+ CD5+ | 1 | (<5%) |

**Table 1.** The percentage of T lymphocytes and the CD4/CD8 ratio were normal. The percentage of T lymphocytes expressing MCH class II HLA-DR antigens and gamma/delta lymphocytes was normal. There was CD57 markers and, partially, also the CD16 and CD56 markers. The percentage of NK cells was normal. There was a slight reduction in the percentage of B lymphocytes.

Five years later the patient was re-evaluated due to an episode of marked telogen effluvium which, when there is no functional alteration of the thyroid, is secondary to thyroiditis caused by increased TSH receptor antibodies.

In the same period, the urticaria resumed during the summer.

Another five years later, she reported a nagging return of urticaria that, after showering, left signs similar to whip marks. During this period she went to the Cardiological Emergency Department due to arrhythmia where it was found that her CPK had increased and troponinemia was normal.

Additionally, she reported paresthesia on the soles of the feet. Through the years the patient often underwent blood chemistry tests and CPK progressively increased.

Considering the CPK values and the symptoms in the lower limbs, additional investigations were planned to evaluate whether this new episode of chronic urticaria was actually chronic urticaria or a symptom of dermatomyositis.

The muscle damage assessed through blood analysis was evident: CPK 639 U/L, aldolase 8.1 U/l (VN 1.0-7.7), LDH 291 U/L (VN 135- 214).

Electromyography (EMG) and electroneurography (ENG) of the lower limbs were within the normal limits.

Analysis of immunological markers in flow cytometry showed a slight increase in the percentage of granular T lymphocytes [Table 1]: a pattern compatible with the diagnosis of chronic lymphoproliferative T-cell large granular lymphocytic leukemia (T-LGLL).

EMG/ENG and muscle MRI were performed before the muscle biopsy and EMG/ENG was found to be within the standard range.

MRI of the lower limbs indicated moderate fibroadipose substitution in the right semitendinosus, gluteus minor and medial muscles, and of the left vastus medialis muscle. Similar aspects, which however were of a lighter entity, bilaterally affected the sartorius muscle and the remaining muscles of the posterior compartment of the thigh. In both legs there was fibroadipose substitution in the gastrocnemius right soleus, left peroneal muscles, and left soleus muscles. At the level of the soleus muscle, the fibroadipose substitution was more evident since it was moderately extended.

Additionally, modest muscle edema was observed in the vastus medialis of the right leg and in the medial gastrocnemius and peroneal muscles but it was less prominent in the soleus of the right leg.

Bilateral peripheral edema was noted in the posterior thigh compartment and on the left there was also some mild intramuscular involvement.

Nothing remarkable was observed for the shoulder girdle and upper limbs.

Since the muscle damage had been documented with a non-invasive technique, a muscle biopsy was performed at the level of the vastus lateralis muscle of the left lower limb so as to better define the type of damage.

Histological examination revealed muscle fibers with diameter of 6 to 64 microns.

Hematoxylin and eosin (H&E), Gömöri's trichrome, PAS, and Oil Red O staining were used for lysosomal acid phosphatase and oxidative reactions were carried out.

H&E showed moderate fibral polydimensionalism due to some atrophic fibers; 4-5% of the fibers had central nuclei. Some fibers were in phagocytosis with small infiltrates of lymphomonocytic elements that had a vesicular nucleus, which were surrounding and sometimes invading some muscle fibers. Gömöri trichrome staining highlighted gradual increased permysial connective tissue. Oxidative reactions emphasized modest subsarcolemmal mitochondrial edges.

PAS stains for glycogen and Oil Red O stains for lipids were normal.

Staining for lysosomal acid phosphatase showed a marked increase in autophagic activity in inflammatory infiltrates and, more modestly, in numerous other fibers.

Histology revealed inflammatory myopathy with isolated fibers in phagocytosis, whereas the diagnosis of inclusion-body myositis was excluded. The search for the micro-rearrangement for the gamma chain of the TCR identified on the DNA extracted from the peripheral blood was positive also on the DNA extracted from the muscle. At the end the anti-CN1A antibodies were tested and found positive.

**Table 2 ANALYSIS OF IMMUNOLOGICAL MARKERS IN FLOW CYTOMETRY ON PERIPHERAL BLOOD**

**White blood cell data after one year of methotrexate therapy**

| ***Test*** | ***Result*** | ***Reference values in peripheral blood*** |
|---|---|---|
| **VBC (x 10^9/L):** | 5,3 | |
| **%** lymphocytes | 46 | |
| Gate | lymphocyte | |
| area analyzed | 42% of total cells | |
| CD3 | 84 | (75% + 7) |
| CD5 | 85 | (75% + 7) |
| CD4 | 67 | (47% + 7) |
| CD8 | 19 | (30% + 6) |
| CD4+ CD8+ | 2 | (<5%) |
| Ratio CD4/CD8 | 3.5 | (1.7% + 0.6) |
| HLA-DR | 9 | (13% + 5) |
| CD8+ HLA-DR+ | 1 | (<5%) |
| CD3+ gammadelta+ | 4 | (4% + 3) |
| CD16 | 12 | (13% + 5) |
| CD56 | 15 | (13% + 5) |
| CD57 | 19 | (15% + 4) |
| CD3+ CD16+ | 3 | (<5%) |
| CD3+ CD56+ | 8 | (<5%) |
| CD3+ CD57+ | 12 | (6% + 3) |
| CD3- CD16+ CD56+ | 8 | (13% + 5) |
| CD3- CD16+ CD57+ | 7 | (<5%) |
| CD56+ CD57+ | 5 | (<5%) |
| CD19 | 5 | (10% + 3) |
| CD19+ CD5+ | 1 | (<5%) |

**Table 2.** The percentage of T lymphocytes and the CD4/CD8 ratio were normal. The percentage of T lymphocytes expressing MCH class II HLA-DR antigens and gamma/delta lymphocytes was normal. Slight increase in the percentage of granular T lymphocytes: these cells coexpress the CD3 and CD57 markers and, partially, also the CD16 and CD56 markers. The percentage of NK cells was normal. There was a slight reduction in the percentage of B lymphocytes.

## Results and Discussion

T-LGLL was first described in 1977 by Mc-Kenna et al. [1] and was believed to be a variant of T-cell or T-prolymphocytic chronic lymphocytic leukemia. Only in 2008 did the World Health Organization include it among mature tumors of type T and NK [2].

Since T-LGLL is a form of leukemia known for its association with autoimmune disorders [1,5], the decision was made to explore whether there was histologically verifiable muscle damage and, if verified, whether it was due to an autoimmune injury.

Our study tried to find whether the patient was suffering from chronic urticaria due to T-LGLL or if she was also affected by dermatomyositis and by T-LGLL.

Histological studies excluded the diagnosis of inclusion-body myositis, characteristic of myositis due to T-LGLL, but the anti-CN1A autoantibody test was positive.

To clarify all this, the search on DNA extracted from the muscle of the micro-rearrangement of the TCR gamma chain which was previously identified on the DNA extracted from peripheral blood—was positive.

It is difficult to classify the myositis in our case in one of the five known groups of idiopathic inflammatory myopathies [6,7] which Bohan and Peter attempted to distinguish in 1975. The classification is still a guide in this complex chapter of dermatology and rheumatology.

In this case, many data contradicted each other. Myositis, appeared at the age of 55-60, usually affects the shoulder girdle and upper limbs [8,9] in our case it did not. This finding prompted us to search for inclusion-body myositis, which had instead been excluded by the histological findings.

The positivity to anti CN1A antibodies led to the diagnosis of inclusion-body myositis [10].

The positivity of the search for the presence in the DNA extracted from the muscle of the micro-rearrangement for the gamma chain of the TCR, that had also been identified on the DNA extracted from peripheral blood allowed us to conclude that myositis could be attributed to T-LGLL.

Thus, the chronic urticaria appeared to have been the skin symptom triggered by T-LGLL prior to the beginning of treatment. Myositis is a disease related to this type of leukemia.

One year of weekly therapy with 10 mg of Methotrexate together with 20 mg of folic acid strongly reduced the symptoms of urticaria. The enzymatic indices of muscle damage normalized, even though there was a slight increase in the percentage of granular T lymphocytes [Table 2].

The disease started about ten years before the diagnosis. After the initial suspicion of chronic urticaria secondary to hematological-oncological disease, the diagnostic hypothesis was changed to dermatomyositis due to reported leg weakness and tripping related to the skin irritation caused by flogged urticaria. Dermato- myositis was excluded by histological and TCR search. The final diagnosis of chronic urticaria was considered secondary to the newly identified form of chronic leukemia, T-LGLL.

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## DECLARATIONS

### Authors' Contribution

Contributed equally to the drafting of manuscript, data collection and analysis:

Floria Bertolini ,Luigi Clauser

### Availability of data and materials

Not applicable

### Financial support and sponsorship

None

### Conflicts of interest

All Authors declared that there are no conflicts of interest

### Ethical approval and consent to participate

Not applicable

## Consent for publication

Written informed consent was obtained for all patient data.

## Copyright



## References

[1] McKenna RW, Parkin J, Kersey JH, GajlPeczalska KJ, Peterson L, Brunning RD. Chronic lymphoproliferative disorder with unusual clinical, morphologic, ultrastructural and mem- brane surface marker characteristics. Am. J Med. 1977, 62(4): 588-596. doi: 10.1016/0002 - 9343(77)90422-3.

[2] Barilà G, Teramo A, Gattazzo C, Zambello R, Semenzato G. Leucemia a grandi linfociti granulari. Ematologia oncologica.it “Diagnosi difficili e rare”. Dynamicon ed. Vol 1 - n.3 – 2014, 49-57.

[3] Dearden C. Large granular lymphocytic leukemia pathogenesis and management. Br J Haematol. 2011; 152(3):273-283. doi: 10.1111/j. 1365-2141.2010.08494.x

[4] Zhang R, Shah MV, Loughran TP, Jr. The root of many evils: indolent large granular lymphocyte leukemia and associated disorder. Hematol. Oncol. 2010; 28(3): 105 – 117. doi: 10.1002/ hon.917.

[5] Rose MC, Berliner N. T-cell large granular lymphocyte leukemia and related disorders. Oncologist,2004; 9(3): 247- 258.

[6] Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975 Feb 13;292(7):344-7. doi: 10.1056/NEJM19750 2132920706.

[7] Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975 Feb 20;292(8):403-7. doi: 10.1056/NEJM 197502132920706

[8] Braun-Falco O, Plewig G, Wolff HH, Burgdorf WHC. Dermatologia ed. Italiana a cura Gelmetti C, Springer-Verlag Italia 2002, 814-818.

[9] Dion E, Cherin P, Payan C, Fournet JC, Papo T, Maisonobe T, Auberton E, Chosidow O, Godeau P, Piette JC, Herson S, Grenier P. Magnetic resonance imaging criteria for dis- tinguishing between inclusion body myositis and polymyositis. J Rheumatol 2002 Sep; 29(9):

1897-906. PMID: 12233884

[10] Tawara N, Yamashita S, Xiao Z, Korogi M, Zhang Z , Doki T, Matsuo Y, Nakane S, Maeda Y, Sugie K, Suzuki N, Aoki M, AndoY. Pathomec- hanisms of anti-cytosolic 5'- nucleotidase 1A autoantibodies in sporadic inclusion body myositis. Ann Neurol. 2017 Apr;81(4):512-525. doi: 10.1002/ana.24919. Epub 2017 Apr 3. Doi:10.1002/ana.24919