International Journal of
Case Reports & Short Reviews

Case Report

Acquired Angioedema and Large Granular T-Cell Leukemia -

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Submitted: 29 December, 2016; **Approved:** 17 February, 2017; **Published:** 20 February, 2017

Citation this article: Postorino M, Pupo L, Guarino MD, Meconi F, Mariotti B, et al. Acquired Angioedema and Large Granular T-Cell Leukemia. Int J Case Rep Short Rev. 2017;3(1): 010-012.

Acquired Angioedema (AAE) is a rare syndrome due to an acquired deficiency of C1 inhibitor (INH), enzyme involved in the regulation of C1 factor activity. C1-INH deficiency leads to C4 and C2 components depletion, while the terminal complement components remain normal. C1-INH deficiency can also be of genetic origin (Hereditary Angioedema, HAE) on the basis either of a defect in an enzymatic function or of a structural deficient gene. The clinical features include subcutaneous nonpruritic swelling, involving face, limbs, genitals, edema of the gastrointestinal mucosa with partial obstruction and consequent severe abdominal pain together with a high risk of death by suffocation due to the obstruction of the upper airways. Clinically AAE and HAE are indistinguishable and the therapeutic strategies are the same in both syndromes. AAE is often associated with neutralizing autoantibodies (autoAb) against C1-INH on the background of a lymphoproliferative disorder, but sometimes autoAb are not found in the serum [1]. We report the case of a patient with AAE, showing a sudden weight gain of about 20 Kg because of a massive generalized edema.

CASE PRESENTATION

In November 2013, a 68 years old patient showed a sudden massive generalized edema involving all the subcutaneous tissues, lips, tongue and a gastrointestinal subocclusion due to mucosal edema. There was no important laryngeal involvement since eight years ago the patient underwent laringectomy for laryngeal cancer. He had no familial history of angioedema and his anamnesis was negative for major allergic episodes. No superficial, mediastinal, abdominal lymphadenopathies were detected at physical examination. Complement activity was tested: C1-INH level was 13,5 mg/ dl (normal 15,4-35,10 mg/ dl); C1q 159 mg/dl (50-250 mg/ dl), CH50 140% (51-150%). The blood count showed only a mild lymphocytosis. The immunophenotypic examination performed by flow cytometry showed an increase of CD3+CD4+ lymphocytes. The morphological examination of peripheral venous smear was characterized by the presence of large lymphocytes with azurofilic granules in the cytoplasm. The diagnosis was large granular T Lymphocytic Leukemia (LGL). The histological examination of the bone marrow showeda slight T-cell infiltrate (30%).The immunocytochemistry revealed a clone with a T cell phenotype ($CD2^+$, $CD4^+$, $CD3^+$, $CD16^+$ and $CD57^-$). A monoclonal profile was found for T cell receptor alpha beta. The percentage of plasma cells in the bone marrow was <1%. Only a slight policlonal hypergammaglobulinemia was observed. Auto-antibodies against C1-INH were absent.

PET/CT scan revealed both a diffuse thickening of the subcutaneous tissues and some laterocervical/ inguinal lymph nodes around 1 cm with slight contrast enhancement, presenting normal morfostructural characteristics and only a mild splenomegaly. Noteworthy, the patient did not use any regular or alternative medication that could unleash AAE.

First treatment was Methylprednisolone at a dose of 1 mg/ Kg/ die for one month and diuretics, but the patient had only minimal clinical response. After one month, we decided to introduce ex iuvantibus administration of C1-INH at dose of 1000 UI 3 times per week. After one month the patient achieved only a partial response obtaining a weight loss of 8 Kg. Three months later the patient showed an increase of white blood cells with T lymphocytosis, although under corticosteroid therapy and subsequently he had a relapse of angioedema with new weight gain and pulmonary subedema (Figure 1). On that occasion he survived the acute laryngeal edema due to previous above-mentioned laryngectomy. In this case, there being no precedent in literature of the association between AAE and LGL, a specific informed consent, created by our legal counsel, was submitted and then was approved by the patient. So we administer single bolus of high dose of Methotrexate [(MTX) 1000 mg total dose)] with leucovorin rescue, again C1-INH for one month and diuretics such as furosemide at 125 mg per day for three days. After the resolution of the swelling which occurred about one month after, this therapeutic scheme was suspended. Subsequently the patient showed a depressive syndrome for which psychological support

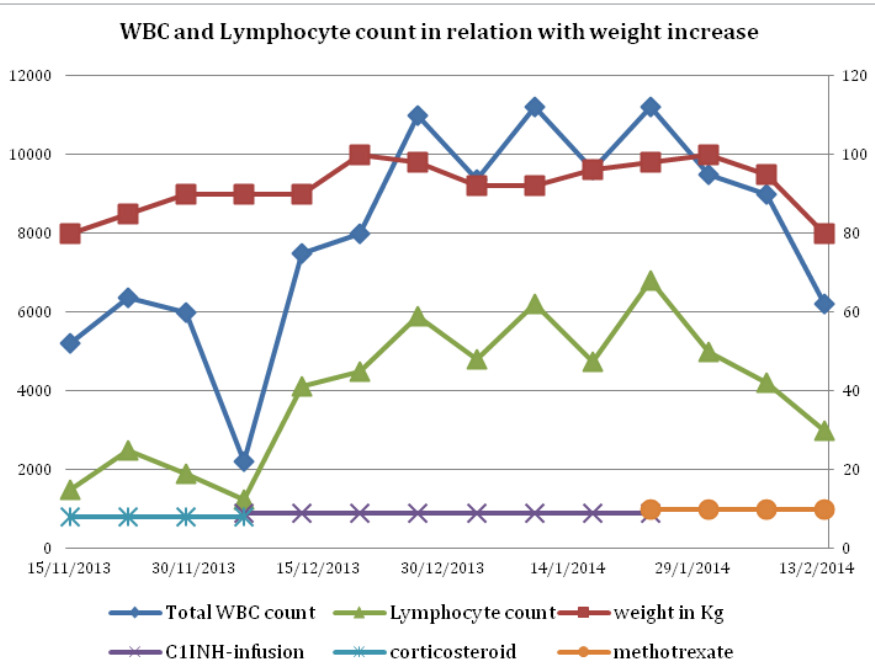

Figure 1: WBC and Lymphocyte count in relation with weight increase.

was necessary. Some months later, the patient showed an episode of Pneumocistis pneumonia, probably due to immunosoppression, which was treated successfully with Bactrim at high doses.

After the resolution of pneumonia and blood count normalization, the patient, showing only a slight relative lymphocytosis, continued MTX 15 mg/ mq/ week until November 2016, without any other angioedema episode.

DISCUSSION AND CONCLUSIONS

Angioedema is usually associated with B cell lymph proliferative disorders often on the basis of auto Ab intervention [2].Acquired angioedema has been associated also with monoclonal gammopathy of undetermined significance secondary to C1 inhibitor deficiencies [3] but there has been only one reported case of peripheral T-cell lymphoma (PTCL) presenting with angioedema, which was published in 1988 [4]. At first, without any recent literature reference concerning the correlation between T lymph proliferative disorders and AAE, we chose corticosteroids and clinical observation as first therapeutical approach. Interestingly, here we reported a rare case of T-cell leukaemia of granular lymphocyte morphology and CD3+CD4+ phenotype [5]. As soon as we observed the first increase in White Blood Cell (WBC) count with lymphocytosis, we considered a possible association between the T-lymphoid clonal population and AAE manifestation, although this was not confirmed in recent literature yet.

The initial corticosteroid therapy induced just a partial response of patient's angioedema. The only data that could hypothesize that angioedema might be a paraneoplastic presentation of LGL was the efficacious ex iuvantibus therapy with MTX plus support therapy with C1-INH. In fact, the success of the therapy with C1-INH was also explained by the absence of neutralizing antibodies against C1-INH complement factor. We still not have clear which was the exact mechanism that led to angioedema, even if it is clear that cytotoxic therapy caused the stabilization of the lymph proliferative disorder and, at the same time, the regression of the angioedema.

In conclusion, we hypothesize that inflammatory activation due to the aberrant expression of some cytokines by subpopulations of lymphocytes might be the cause for C1-INH consumption and subsequent angioedema event.

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