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Idiopathic CD4+ Lymphocytopenia Associated with Evans' Syndrome: A Case Report

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Abstract Idiopathic CD4+ lymphocytopenia (ICL) is a syndrome first defined in 1992 by the Centers for Disease Control and Prevention (CDCP) as "a documented absolute CD4 T lymphocyte count of less than 300 cells per cubic millimeter or of less than 20% of total T cells on more than one occasion, no evidence of infection on HIV testing and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells". The clinical course, immunologic characteristics, CD4 T cell kinetics, long term outcome and prognosis of this syndrome remain poorly defined but it is widely accepted that ICL is a rare, heterogeneous syndrome, usually detected after the occurrence of an opportunistic infection in a person without known immunodeficiency or immunodepression although it can also be an incidental laboratory finding. Autoimmune phenomena are common in this syndrome. In this article, we reported a case diagnosed with an Evans' syndrome and that fulfilled the CDCP definition of ICL.

Keywords: *thrombocytopenia, anemia, immune defeciency, Fow cytometry*

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1. Introduction

Clinical presentation of idiopathic CD4+ lymphocytopenia differs widely from clinically mild phenotype to severe infections or disseminated neoplasms.

Various auto-immune and immunodeficiency complications were reported suggesting the role of an immune mechanism in the pathogenesis of ICL.

We reported a case of a long term Evans syndrome in an ICL patient with a very low CD4+ T cell count.

2. Case Presentation

A 30-year-old Tunisian man presented in October 2007 with a one week history of fatigue and skin pallor. He was born from a consanguineous marriage. His mother has rheumatoid arthritis. He had no known risk factors for HIV-infection and his medical history was unremarkable, in particular, he had neither clinical condition of congenital immunodeficiency nor opportunistic infection.

On admission, the patient had an hemolytic anemic syndrome. Nor hemorrhagic and infectious manifestations or tumor syndrome were noted. The hemoglobin level was 9 g/dl and the blood counts were as follows: platelets 130000/mm^3, leukocytes 5900/mm^3 and lymphocytes 1000/mm^3. The serum levels of bilirubin and LDH were elevated.

An Evans' syndrome was suspected and a Coombs test (IgG and C3) was positive whereas antiplatelets antibodies were negative.

Therapy with steroids was started but the anemia persisted. Human Immunoglobulin with bolus of steroids was indicated and led to a clinical and biological improvement. His hemoglobin level reached a normal range but Platelet and lymphocyte counts persisted under normal. He didn't present any infectious disease. Blood cell counts outcome are in Table 1.

A second episode of bicytopenia occurred heitheen months later, followed by an episode of pancreatitis. Etiologic investigation of this Evans syndrome included normal chest radiography and computed tomography scan, a screening for other autoimmune disorders which concluded to negative Anti-Endomysium Antibodies, Anti Peroxydase Antibodies, Antigliadine Antibodies, Anti Thyroglobuline Antibodies and Anti nuclear antibodies. Anti Phospholipid Antibodies and Anti Smooth Muscle Antibodies were positive. HIV polymerase Chain Reaction assay was negative. B and C Hepatitis serologic tests were also negative. Bone marrow smear and biopsy showed no abnormality. EPP was normal with normal rate of IgG, IgM, and IgA.

Table 1. Patient's blood cell counts

	9/1O/07	10/12/07	21/01/08	15/05/08	17/04/09
Hemoglobin level g/dl	9	14.2	15.5	16	11.9
WBC/mm3	5900	10900	9300	7000	10200
Lymphocytes/mm3	1000	872	1023	1260	1000
Platelets/mm3	130000	125000	111000	130000	30000

Table 2. Patient's Flow cytometry immunophenotyping of peripheral blood lymphocytes

Cell Type	April 2009	May 2009	Normal Values (cells/mm^3)
Total lymphocytes	1000	900	1500-3000
LB:CD19,CD20	67	57	50-400
NK:CD16,CD56	75	75	80-350
TL:CD3,CD5	690	600	1080-1980
CD4	100	80	330-670
CD8	590	520	780-1300
Ratio CD4/CD8	0,16	0.15	1.5-2.5

Flow cytometry immunophenotyping of peripheral blood lymphocytes was investigated in order to analyze monoclonality of B or T cells and showed a decreased ratio of the CD4/CD8 cells with a surprising low count of CD4+ T cells which was confirmed at 2 occasions Table 2.

3. Discussion

Our patient presented with autoimmune haemolytic anaemia (AIHA), autoimmune thrombocytopenia (AITP), T lymphopenia and positive antiphospholipid and antitissue antibodies. He also fulfills the CDCP definition of ICL (CD4+ count of less than 300 × 10^6/L on two occasions in the absence of HIV infection or other known causes of immunodeficiency).

Although the diagnosis of ICL was done one year after the diagnosis of Evans' syndrome, lymphopenia was present from the beginning of the autoimmune manifestation.

The presence of positive anti tissues and anti phospholipid antibodies in this patient further lends support for an autoimmune phenomenon in conjunction with his Evans' syndrome.

A differential diagnosis between a primary Evans' syndrome and a secondary Evans' syndrome following ICL could not be made initially.

In this case and according to the literature ICL syndrome, CD4+T lymphocytopenia may be accompanied by lymphocytopenia of CD8+ T, B or NK cells) [1,2]. In patients with idiopathic thrombocytopenia, a reduced ratio of CD4/CD8 cells was reported, with an improvement of this ratio in remission [3]. ICL Lymphopenia could be associated with a variety of human autoimmune diseases such as lupus, Sjögren's syndrome,thyroiditis, vitiligo, vasculitis, and Antiphospholipid syndrome [4] but the temporal relationship of autoimmune disease and ICL and the exact nature of correlation of the 2 diagnoses could not be concluded [5,6]. In a study of 214 Sjogren's patients, 3.7% were found to have ICL lymphocytopenia associated with antibodies directed against CD4 lymphocytes [5,7].

Recent finding suggests that pathogenic mechanisms implicated in ICL include:

- An unbalance between the regulatory and conventional T-cell compartments, triggering the development of autoimmune disorders [8].
- Genetic mutations such as mutations in major histocompatibility complex class II, missense mutations in RAG1 and Unc119. [9,10])
- Cytokines release of IL21 and decrease of IL2 and IL7. [9,11]

The evolution of the ICL remains poorly known in the absence of important follow-up cohorts. It appears that this lymphopenia is usually persistent and stable, even if spontaneous corrections are possible. Clinically, the onset of opportunistic infections is not predictable [6,10].

4. Conclusions

The mechanisms that may result in ICL lymphopenia are multiple. If a particular clinical context is not found, it is necessary to know to seek infectious, dysimmune or neoplastic etiology. After negative conducted investigations, idiopathic CD4 + lymphopenia should be considered in order to adapt the follow-up of these patients.

Lymphopenia has long been associated with autoimmune manifestations. Thus, it is necessary to look for a lymphopenia in front of certain situations of autoimmunity.

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