Table of Contents

Original Articles

Cytomorphologic Spectrum of Hurthle Cell Lesions of Thyroid: A Study of 54 Cases .................................................................06
K.R. Anila, Nileena Nayak, Preethi Sara George, K. Jayasree

Rosai–Dorfman Disease – Five Years Retrospective Analysis from Tertiary Cancer Center ..........................................................11
K. Aradhana, B. Thjaswini, Shamsundar, R. Nanda, Usha Amritham, G.V. Giri

Lung cancer epidemiology among the Bahraini population, 1998–2011 ..............................................................................18
Najat Mohamed Abulfateh, Randah R. Hamadeh, Majida Fikree

Epidemiology of Colorectal Cancer in Iraq, 2002–2014 ..............................................................................................................23
Safaudeen Abdulrahman Al Dahhan, Faris H. Al Lami

Profile of High Grade Gliomas – A Single Center Experience .................................................................................................27
Basharat Mujtaba Jan, Arif Hussain Sarmast, Abdul Rashid Bhat, Altaf Rehman Kirmani

Assessment of Sunitinib Alternative Prescription Schedules in Metastatic Kidney Cancer: A Study of 10 Cases .........................33
Habib Diallo, Hasnae Alaoui Mhamdi, Salma Elouarzazi, Mohamed Fadli, Rhizlane Belbaraka

Human Papilloma Virus (HPV) in Sinonasal Papillomas and Squamous Cell Carcinomas: A PCR–based Study of 60 cases ..........37
Ambreen Beigh, Ruby Reshi, Sheikh Junaid, Mehnaz Sultan Khuroo, Summyia Farook

Cancer Statistics in Giresun Province, Turkey: a 12–Years Retrospective Review .................................................................43
Ayşegül Çebi, Egemen Akgün, Tuncer Öztürk, Esin Avc

Review Article

Risk Factors of Cancer in the United Arab Emirates ..................................................................................................................49
Hira Abdul Razzak, Aliya Harbi, Wael Shelpai, Ahmad Qawas

Case Reports

Lymphoid Proliferation in Eyelid: A Primary follicular lymphoma case ..................................................................................58
Deivy Cruzado-Sánchez, Walter Andree Tellez, Solon Serpa–Frias, Grisnery Maquera

Transanal Minimally Invasive Surgery (TAMIS), First in Kuwait: A Case Report .................................................................61

Tumor Recurrence at Donor Site of Pectoralis Major Myocutaneous Flap with Tumor–free Primary Oral Carcinoma ..................64
Rakesh Kain, Suvashis Dash

Vaginal Metastasis of Renal Clear–cell Cancer ................. .................................67
Rehalia—Blanchard Amel, Morel Adeline, Rancoule Chloé, He MingXuan, Magné Nicolas, Falkowski Sabrina

T cell Large Granular Lymphocytic Leukemia with Pulmonary Hypertension .............................................................................72
Sidra Khalid, Hamed Daw, Miriam Jacob, Megan Nakashima

Fatal Outcome of Recurrent Infantile Pelvic Desmoid Tumor Treated with Tamoxifene ..............................................................75
Lamiae Amaadour, Zineb Benbrahim, Othmane Zouiten, Nezar Bourdi, Youssef Lamrani Alaoui, Asmae El Mazti, Nawal Hammae, Nawfel Mellas

Conference Highlights/Scientific Contributions

• News Notes ..........................................................................................................................79

• Advertisements ..................................................................................................................83

• Scientific events in the GCC and the Arab World for 2018 ..................................................................................................84
Case Report

**T cell Large Granular Lymphocytic Leukemia with Pulmonary Hypertension**

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**Abstract**
T cell large granular lymphocytic leukemia is a hematological disorder which is characterized by the proliferation of CD 3+ cytotoxic T cells. We present a case about a patient who was diagnosed with T cell large granular lymphocytic leukemia and then developed pulmonary hypertension. He was treated for his leukemia with methotrexate and simultaneously treated for his pulmonary hypertension with selexipag and ambrisentan. As his leukemia improved, we also noticed an improvement in his pulmonary hypertension from a NYHA class IV to class I. Hence, we believe there is an etiopathological link between the T cell large granular leukemia and associated pulmonary hypertension.

**Keywords:** T cell LGL leukemia, pulmonary hypertension, methotrexate.

**Introduction**

T cell large granular lymphocytic (LGL) leukemia is a clonal proliferation of CD 3+ cytotoxic T cells. A majority of cases show a CD 3+, TCR αβ, CD4-, CD5dim, CD8+, CD16+, CD27-, CD28-, CD45R0-, CD57+ phenotype. On presentation, many patients are symptomatic, with splenomegaly occurring in 25% to 50%, recurrent infections and neutropenia in 15 to 56%. Infections mostly involve the mucocutaneous or respiratory system (1). It is associated with autoimmune and other hematological disorders. In a French cohort, pulmonary arterial hypertension occurred in 2/229 cases (2). We present a case, which highlights the onset and progression of T cell LGL leukemia associated with pulmonary hypertension.

**Case Presentation**

A 37-year old male presented with recurrent serous otitis media, intermittent shortness of breath, rash on his extremities and fatigue for one month in an outpatient setting. Past medical history was significant for childhood bronchitis and bilateral carpal tunnel syndrome. He smoked about 1 ppd for 20 years with occasional marijuana use. On physical examination, vital signs were unremarkable and the pertinent finding was a maculopapular rash on both arms. Labs were significant for wbc count of 2.1 k/uL, haemoglobin of 16 g/dL, and platelets of 106 k/uL. He was referred to hematology and oncology for leukopenia and thrombocytopenia. On physical examination, he had splenomegaly. The cause of neutropenia was attributed to hypersplenism and since the patient had an ultrasound of the liver suggestive of hepatitis seven years ago, work-up for autoimmune hepatitis was included. Repeat cbc showed wbc count of 1.6 k/uL, haemoglobin of 15.3 g/dL, platelets of 94 k/uL, ANC 0.5 k/uL, and absolute lymphocyte count of 0.8 k/uL; further autoimmune and infectious work up was negative for ANA, hepatitis A, B, C, RA factor and HIV. Peripheral blood interpretation included a relatively increased CD4+ T cells immunophenotypically consistent with T–cell large granular lymphocytes (Fig. 1). Cytogenetic test showed a normal karyotype, 46 XY, and an increased CD4:CD8 ratio. The bone marrow biopsy had neutrophilic cells with
decreased CD 11b, no increase in blasts (2%). T cell gene rearrangement by PCR detected clonal T cell receptor beta gene rearrangement. Cytophenetics of bone marrow revealed no evidence of an acquired clonal abnormality. The bone marrow aspirate had normocellular marrow with normal maturation, absolute neutrophilia, lymphopenia and thrombocytopenia. Flow cytometry showed lambda-bearing cells with no evidence of monoclonality or immature lymphoid phenotype; the CD4 to CD8 ratio was increased with mixed cellularity (13.32). At that time, all the investigations supported a working diagnosis of T cell LGL leukemia and the plan was to observe with CBC every 4 weeks.

Subsequently, he had shortness of breath for two weeks and then had a syncopal episode due to which he was hospitalized. His electrocardiogram showed T wave inversions in V3 to V5, right ventricular hypertrophy and right axis deviation. Echocardiogram was performed and there was normal left ventricular function (EF 58%) with signs of pulmonary hypertension including right ventricular dilation, right ventricular systolic pressure (RVSP) of 106 mmHg, moderate pulmonary valve regurgitation and severe tricuspid valve regurgitation. Further work-up of pulmonary hypertension was undertaken. Monoclonal protein, cryoglobulin, CANCA, p–ANCA, proteinaise–3 antibody, MPO were negative. He had an elevated IgG of 1450 mg/dL. His ACE level was 93 U/L. VQ scan showed a low probability of pulmonary embolism. CT scan of the lungs ruled out pulmonary embolism and pulmonary veno–occlusive disease. PFTs were significant for reduced DLCO. Cardiac enzymes were negative. NT proBNP was 4610 pg/mL. He underwent right heart catheterization, which showed a mean pulmonary artery pressure of 61 mmHg, mean pulmonary capillary wedge pressure of 8 mmHg, pulmonary vascular resistance (PVR) of 10 Woods units, and a preserved thermomodulation cardiac output. The inhaled nitric oxide vasoreactivity test was negative. He was NYHA class IV. The 6-minute walk test was 910 ft. He improved to NYHA class I with NT proBNP of 311 pg/mL and RVSP of 70mmHg on echocardiogram.

**Discussion and Conclusion**

T cell LGL leukemia accounts for about 2 to 5 % of chronic lymphoproliferative disorders in North America, with an incidence of 1 in 10 million people (3). Only 20 to 25% of patients younger than 50 years are affected (1).

There are two variants of T cell LGL leukemia, which are indolent and aggressive. The indolent subtype occurs in 85% of all cases (2). The clinical presentation is usually with recurrent bacterial infections, cellulitis, perirectal abscesses, respiratory infections, cyclic neutropenia, fatigue due to anemia, or B symptoms (fever, night sweats, weight loss) (3).

Neutropenias are found in 80% of the cases. The underlying mechanisms are direct destruction of myeloid precursors with infiltrating leukemic cells, dysregulation of maturation of myeloid cells, antibody—or immune complex—mediated peripheral destruction of neutrophils, or induction of apoptosis of neutrophils through Fas/Fas ligand pathway. Thrombocytopenia occurs in 20%, which is attributed to inhibition of megakaryopoiesis, antibody—mediated destruction of platelets, and splenic sequestration (4).

The etiology is unknown. LGL survival is promoted by platelet derived growth factor and interleukin–15, which causes dysfunction of apoptosis by affecting the pathways that activate cell death. There is activation of JAK2/signal transducer and activator transcription 3/Mcl–1, RAS/MAKP, and SFK/P13K/AKT and sphingolipid signalling pathways (1). In terms of cytogenetics, indolent T cell LGL leukemia mostly has a normal karyotype (4).

Diagnosis is based on LGL in the peripheral blood. They display a large size (15–18 µm), abundant cytoplasm with azurophilic granules, and a reniform or round nucleus. The LGL count in the peripheral blood can range from 0.4–2 x109/L. TCR γ PCR is used to determine T cell clonality.
The Vβ TCR repertoire analysis with flow cytometry is also used to demonstrate clonality (1). In the French cohort, 43 patients had Vβ repertoire analyzed; this resulted in a unique Vβ monoclonal proliferation (n=38), defective subset (n=3) and biclonal (n=2) (2). Bone marrow can be hypocellular, normocellular or hypercellular, with the monoclonal LGLs usually involving <50% of the nucleated cells (4). Bone marrow biopsy with immunohistochemistry reveals lymphoid interstitial infiltration with linear arrays of CD 8+, granzyme B, perforin, and/or TIA–1 positivity, which supports the diagnosis (1).

Treatment is only started for symptomatic patients. There is no standard treatment for T cell LGL leukemia. Monotherapy with steroids temporarily improves symptoms and neutropenia, but remissions are not sustained. It is used mostly as adjunctive therapy with immunosuppressants to achieve rapid hematological improvement. The immunosuppressants mostly used are methotrexate, cyclophosphamide and cyclosporine. In the French cohort, the overall response rates were 55% and 67% for methotrexate and cyclophosphamide respectively. Patients who failed to respond to methotrexate were given cyclosporine and 11 out of 15 responded, especially in patients with HLA DR4 phenotype (2). Alemtuzumab, an anti–CD52 monoclonal antibody, in a phase 2 single arm trial showed a 56% haematological response at 3 months (6). Fludarabine when used in 6 patients with T cell LGL leukemia resulted in 100% haematological response and 83.3% complete molecular response (7).

In our case, we believe that there is an etiopathological link between T cell LGL leukemia and pulmonary hypertension. The pulmonary hypertension started with T cell LGL leukemia onset and progression and it improved when methotrexate and prednisone were started for treatment of the leukemia. There are two possible mechanisms in T cell LGL leukemia that can cause pulmonary hypertension. 1) In T cell LGL leukemia, there is dysregulation of Fas–mediated pro–apoptotic pathway which results in increase Fas ligand in patient’s serum. This Fas–ligand can bind to the Fas receptors on the pulmonary endothelial cells and induce apoptosis. 2) The T cell LGL can have a direct cytotoxic effect on the pulmonary endothelial cell line CRL–2898. Cytotoxicity of the leukemic cells is activated by stimulation of surface NKRs–CD158b and CD 94, which in turn activates transmembrane adaptor proteins DAP10 and DAP12. This in turn activates two intracellular signalling pathways: Ras/MEK/ERK and phosphatidyl inositol–3–kinase/MEK/ERK which provides Fas–mediated apoptotic resistance to leukemic cells and enhance cytolytic activity against pulmonary endothelial cells, respectively. Tipifarnib is a farnesyltransferase inhibitor, which inhibits Ras kinase and can lead to decreased cytolytic activity of leukemic cells. Therefore, in our case when the patient’s T cell LGL leukemia was treated with methotrexate and prednisone along with specific treatment for pulmonary hypertension, there was an improvement of pulmonary hypertension as patient’s NYHA class IV improved to class I in five months (7).

T cell LGL leukemia has an indolent course with median survival time >10 years (4). Further prospective studies are required to study the disease course, associated disorders, and targeted therapies to maintain or induce complete remission. Through our case and literature review, it is suggested that the treatment of the leukemia leads to improvement of pulmonary hypertension. Therefore, further investigation is needed to assess this phenomenon.

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