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Developing Hemophagocytic Syndrome during the transformation of Chronic Lymphocytic Leukemia: Case reports of t(7;14), t(14;19) and deletion of 17p

Tarik Onur Tiryaki[1*], Sezen Genc[1] , Gulcin Bagatir Ozan[2], Kivanc Cefle[2], Sukru Palanduz[2], Gulcin Yegen[3], Oner Dogan[3], Meliha Nalcaci[1]

Abstract

Chronic lymphocytic Leukemia (CLL) is the most common form of leukemia in adults. Clinical findings may broad range vary. Detecting some deletions using the FISH method may help us to foresee the progression of the disease and to choose a better treatment method in healing the patient. In this case report, we will present you a CLL patient with t(7;14), t(14;19) and 17p deletions, which are known for bad prognosis, developing autoimmune hemolytic anemia which is refractor to the treatment. This patient unfortunately died due to a clinical form of hemophagocytic syndrome including prolymphocytic transformation.

Keywords: Chronic lymphocytic leukemia, hemophagocytic syndrome, t(7;14), t(14;19), 17p, deletion

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. It's a type of cancer that starts in cells that become certain white blood cells (lymphocytes) in the bone marrow. The cancerous starts in the bone marrow then cancer cells passes into the blood. The frequency of chronic lymphocytic leukemia (CLL) increases in elderly people. Only the 10 % of these patients are younger than 55. This disease is a hematological malignancy which has varying clinical findings. Some genetical abnormalities are associated with bad prognosis. Especially, 11q, 13q, 17p deletions and trisomy 12 are important for prognosis (1, 2). Firstly, 17p deletion was diagnosed in our patient using FISH method. The patients with 17p deletion show bad prognosis and do not respond well to the conventional treatment (2). Chemotherapy of FC was implemented to patients with 17p deletion, high grade disease and showing systematic symptoms. For those patients fludarabine - cyclophosphamide and rituximab (FCR) is accepted as the first line therapy (2). However conventional chemotherapy is poor for those patients having 17p deletion and bad prognostic features (2). In our patient, FC therapy was ceased due to AIHA development after the 2nd cure. The response to therapy is poor for those who develop AIHA during CLL. For those CLL patients, chemotherapy or monoclonal antibody is necessary (3). Bone marrow evaluation and conventional cytogenetic analysis which are not necessary for diagnosis of CLL, should be implemented for the refractory and recurring diseases (1).

Case

A-51-year-old male patient appealed to the clinic with dyspnea with effort, headache, fatigue and pain in the left hypochondria on April, 2015. Patient had type 2 Diabetes Mellitus and hypertension. In physical examination, the patient was pale, had giant splenomegaly and 1 cm lymphadenopathy on right cervical lymph node. The laboratory findings were; Hb:10.6 g/dl, Hct:%33, MCV:87 fl, leukocyte:78.400/mm^3, platelet:44.100/mm^3, monocyte:22.400/mm^3. On the peripheral smear examination there were small mature lymphocytes, big lymphocytes with wide cytoplasm and smudge cells. In addition; reticulocyte rate was %0.8, glucose:89 mg/dl, creatinine:1mg/dl, urinary acid:11.6 mg/dl, LDH: 479 U, total protein:6.5 g/dl, albumin: 3.95 g/dl, gamma globulin:0.46 g/dl. On abdominal ultrasonography spleen was 260 mm and the flow cytometry revealed B cell chronic lymphocytic leukemia with CD5 (+), CD19 (+), CD20 (+), CD23(+). Cytogenetic examination showed %10 of 17p deletion. PET-CT showed cervical, axillar, mediastinal, inguinal and multiple lymphadenopathies in abdomen and splenomegaly. It was evaluated as RAI grade 3 and fludarabin- cyclophosphamide (FC) chemotherapy medication was implemented to the patient. Herpes virus and pneumocystis jiroveci pneumonia prophylaxis was added to the treatment. Despite two cures of chemotherapy leukocytosis and lymphocytosis were still present. FC treatment was stopped due to coombs positive autoimmune hemolytic anemia (AIHA) before the third cure of

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1 Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Istanbul, TR
2 Istanbul University, Istanbul Faculty of Medicine, Department of Genetics, Istanbul, TR
3 Istanbul University, Istanbul Faculty of Medicine, Department of Pathology, Istanbul, TR
*** Corresponding Author:** Tarik Onur Tiryaki **E-mail:** tonurtiryaki@gmail.com **Phone:** +90 (506) 216 86 95

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chemotherapy dated on July 2015. Bone marrow aspiration was made and showed hypercellular marrow with 20 % of fat tissue, hyperplasia of erythroid series, regression of granulocytic series, neoplastic tiny lymphocytic infiltration which showed us interstitial type of CLL. t(7;14), t(14;19) were diagnosed by conventional karyotype. Addition of these two translocations to 17p deletion was evaluated as complex karyotype.

No relative donor was found for allogenic bone marrow transplantation. The patient disagreed to have transplantation from a non-relative donor. Ibrutinib treatment was planned. While this drug was waiting for approval, cyclophosphamide-vincristine and prednisolon (COP) chemotherapy was given to this patient. Partial recovery was observed after this treatment. However, hemolytic anemia developed again after the second cure of COP. The patient's general situation was not suitable for splenectomy. Therefore we gave pulse steroid for three times and rituximab weekly. However, no improvement on AIHA was observed. On November 2015; treatment of 420 mg/day ibrutinib was given via IV.

On the first month of ibrutinib, the spleen length reduced to 11 cm. There was no transfusion demand anymore.Steroid treatment was stopped gradually when hemoglobin level was over 9 g/dl. At that time; some laboratory findings were; leukocyte:4900/mm^3, neutrophil:3800/mm^3 and platelet:186000/mm^3. On the 45th day of ibrutinib treatment; obvious anemia and thrombocytopenia occurred. Due to cytopenia, refractory infections developed. Ibrutinib treatment was stopped. The spleen got bigger in size very quickly; ferritin level progressed to 28000 ng/ml, triglyceride was 350 mg/dl, fibrinogen was 176 mg/dl. Fever, splenomegaly, cytopenia, hypertriglyseridemia and elevated ferritin levels were evaluated as hemophagocytic lymphocytosis (HLH). High dose of dexamethasone treatment. On the control bone marrow smear; transformation of prolymphocytic leukemia was diagnose was started. At this time, 17p deletion was 76% positive, t(7;14) and t(14;19) were still present, as well. The patient died after the first week of the diagnoses of HLH related CLL. The survival life span was estimated as 10 months after the disease was diagnosed.

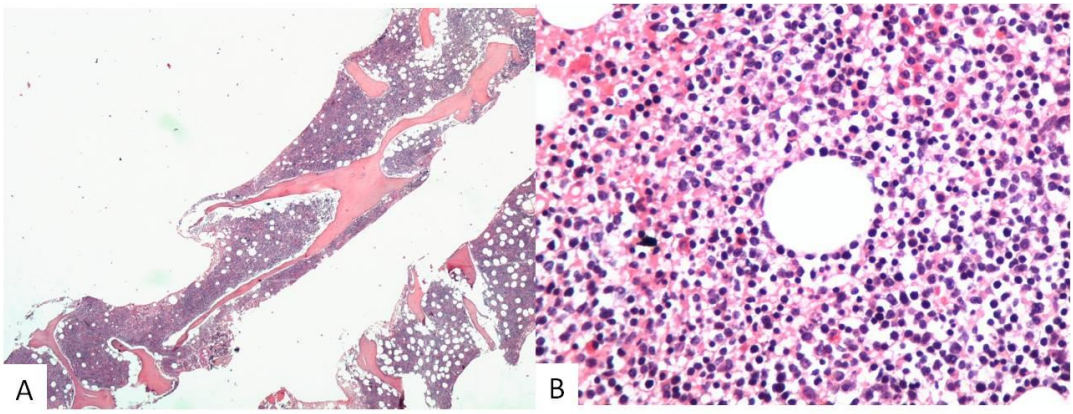

Figure 1: Low magnification view of hypersellulary bone marrow (A). At high magnification interstitial small lymphocytic infiltration is seen (B)(H&E, 4X and 40X magnification respectively)

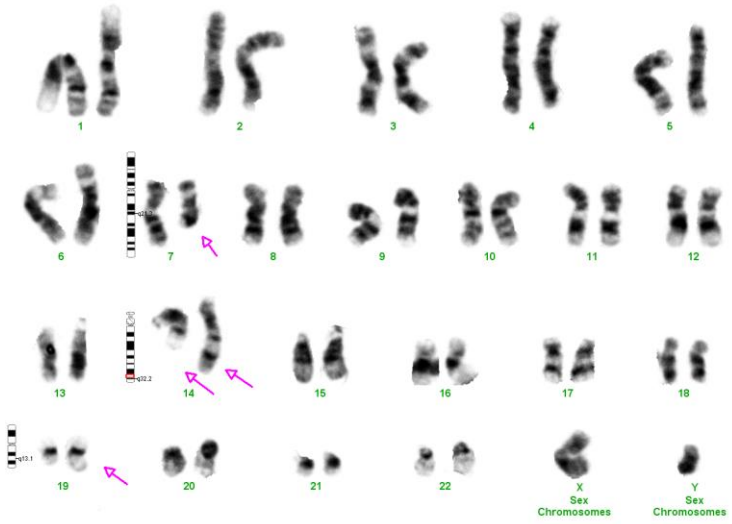

Figure 2: 46, XY, t(7;14) (q22; q32), t(14;19) (q32; q13)

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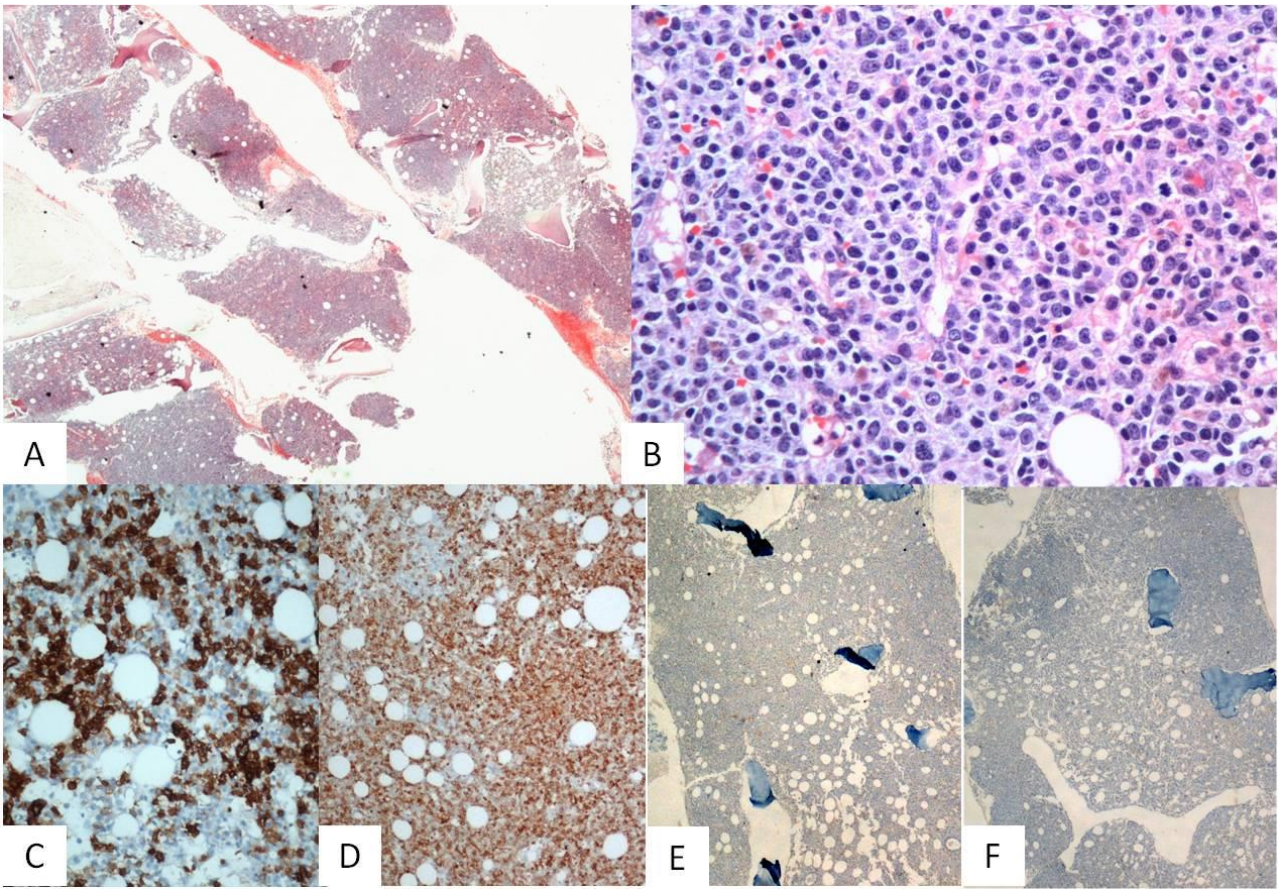

Figure 3: Bone marrow is hypercellulary (A) (H&E, 4X). High power view of H&E stained section reveals nearly diffuse infiltration of prolymphocytes (B). Immunohistochemically neoplastic cells were positive with CD20 (C), CD5 (D) and negative with CD23 (E) and cyclinD1 (F)

Discussion

In our patient, bone marrow was evaluated on the refractory period of the disease. Conventional cytogenesis, t(7;14) and t(14;19) was revealed in addition to signs consistent to chronic lymphocytic leukemia. It was reported that t(14;19) is rare in B cell malignancies. It was again reported that the frequency of the togetherness of young patients, aggressive clinical prognosis and complex karyotype is high. It was announced that this translocation was present in one CLL patient during transformation period to prolymphocytic leukemia (4,5,6,7). The t(7;14) is a rare disorder mostly seen in T cell malignities (8). The genetic features evaluated as complex karyotypes in our patient suggested that the disease would show bad clinical progress. To determine the prognosis of the disease in relapsing refractory CLL patients, complex karyotype is much more meaningful compared to 17p deletion that is presented with FISH method.

Treating those patients who have bad prognostic features with intense treatments and bone marrow transplantation are being discussed (9). Because of this, it was planned to change the medication to ibrutinib. It is well known that ibrutinib is the first line therapy for those who have bad prognostic features (2). In our patient, CLL and AIHA developing seconder to CLL were partially controlled using ibrutinib. Treatment with ibrutinib was permanently stopped due to refractory infections and severe thrombocytopenia, although the patient showed partial response to treatment with aforementioned agent. Lack of treatment caused progression of the disease resulting in prolymphocytic transformation and hemophagocytic syndrome in a very short time. Hemophagocytic syndrome is usually seen in malignancies and inflammations in elderly patients. HFH accompanying CLL had been reported in two patients before (10). The total survival period was 10 months in our patient.

Conclusion

For convenient treatment approaches, the 17p deletion should be searched in newly diagnosed CLL patients using FISH method. If response can not be obtained orin early recurrences it is beneficial to analyze the patient for conventional cytogenetic abnormalities. It would be suitable to start the new treatment methods when complex karyotype is found. The refractory CLL patients should be evaluated for HLH when they develop unexplained fever and in declining cytopenia.

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Ethical issues: All Authors declare, Originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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