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Review Article

Coexistence of Chronic Lymphocytic Leukemia with Hematological Malignancies and Solid Cancers within the Same Patient

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Abstract

Chronic lymphocytic leukemia (CLL) is the most common type of leukemias in the elderly in Western world. Many more studies demonstrated the coexistence or sequential occurrence of CLL with mature chronic lymphocytic malignancies such as Lymphomas, Hairy cell leukemia (HCL), Multiple Myeloma (MM) and with myeloid malignancies including Acute Myeloid Leukemia (AML), Acute Promyelocytic Leukemia (APL), Chronic Myeloid Leukemia (CML), Primary Myelofibrosis (PMF), Essential Thrombocythemia (ET), Polycythemia Vera (PV) and Myelodysplasia (MDS) within the same patient. There was no study seen on coexistence of CLL with acute lymphoblastic leukemia (ALL). Studies have also demonstrated that CLL increases the incidence of some types of solid cancers in the same patient.

Such phenomena have arisen important questions on such complex disease feature 1) about the clonal origin of these cancer cells and 2) on diagnosis and differential diagnosis with different type of malignancies either in liquid or solid form and 3) what treatment strategies should be used for such complex malignancies. Increased disease susceptibility by cancer genes in CLL interacting with other cancer genes, and genomic variation, deficiency/loss of cancer suppressor gene and even through the process of germ line mutation could be the factors in the pathogenesis of such complex diseases.

The aim of this literature review on the association of CLL with haematological malignancies and solid cancers within the same patient is to try to increase the awareness for haematologists and oncologist in such CLL associated malignancies.

In addition, such study will increase the understanding in disease mechanism with new insights, help clinical therapeutical strategies toward to the precision medicine. Potentially, it may provide some clues in related diseases research fields.

It is hope that genomic studies on such complex diseases will reveal the mysteries in the mechanism and proper care will be achieved by the precision medicine in future.

Keywords: *Chronic Lymphocytic Leukemia; Myeloproliferative Neoplasms; Chronic Myeloid Leukemia; Solid Cancers; Clonal Evolution; Precision Medicine*

Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the Western counties than in Asia with highly heterogeneity. CLL is characterized by a relatively stable genome in comparison with other types of hematological malignancies or solid cancers.

Studies showed that deletion of chromosome 6q, 11q, 13q, 17p and trisomy chromosome 12 are the most common cytogenetic abnormals in more than 80% of CLL can be detected by using the traditional cytogenetic and cytogenetic techniques and such abnormalities have become the diagnostic, therapeutic and prognostic factors clinically [1].

Some new mutations such as NOTCH1, SF3B1, BIRC3 FBXW7, MYD88, XPO1 and TP53 associated to patients with CLL have been identified by the next generation sequencing technologies from the genomic level [2-4]. Four risk subgroups (high risk, intermediate risk, low risk and very low risk) have been classified from the genomic level. The identified mutations also can be used for disease stratification clinically [5].

Advance studies provided the molecular evidence of the association of CLL in germ line mutations through the process of telomere dysregulation in CLL development by whole exome sequencing (WES) technology [6].

However, coexistence of CLL or co-occurrence with several different types of haematological malignancies and solid cancers within the same patient have been reported and described in different words such as, co-occurrence, sequential occurrence, concomitant, synchronous occurrence, simultaneous occurrence, subsequent occurred, appearance and disappearance to describe the different sequence occurred in the same patient.

By definition, coexistence or co-occurrence means CLL and other type of disease were diagnosed in the same time within the same patient but it does not tell which one occurs first.

The aim of this literature review is to summarise the association of CLL with those haematological malignancies and some types of solid cancers reported to increase the awareness.

Progresses in mutation gene sequencing diseases toward the precision medicine will improve CLL associated diagnosis and management and it may provide some clues in cancer susceptibility associated diseases/disorders.

Coexistence of CLL with other types mature lymphoid haematological malignancies within the same patient

Coexistence of CLL with other types of mature chronic lymphocytic malignancies have been reported including Hodgkin's disease, HCL and MM.

Coexistence of CLL with Hodgkin's disease (HD)

HD is also called as Hodgkin' lymphoma and the coexistence of CLL with Hodgkin's disease within the same patient have been reported from literatures.

A case of coexistence of CLL and Hodgkin's disease was reported from a research group and that patient was treated but failed. Autopsy confirmed the diagnosis of co-existence of CLL and lymphoma [7].

Choi group reported two cases with coexistence of CLL and Hodgkin's disease. The lymphocytic cell marker analysis was performed on these two cases and their results suggested these two cases were separate and unrelated lymphoproliferative diseases [8].

Coexistence of CLL with hairy cell leukemia (HCL)

HCL is a type of slow growth cancer from B cells named by the appearance of hairy under microscope.

Reported an elderly male patient with a synchronous clone of CLL/HCL and reviewed other 5 elderly male cases published. Their results suggested a controversial conclusion about if CLL and HCL were from the same clone [9].

Reported an elderly male patient of coexistence of CLL and HCL with two distinct abnormal clones of mature B cells by Flow cytometric analysis. Patient was treated by two different strategies; chemotherapy with fludarabine and Cytoxan and monotherapy with rituximab [10].

Studied each separated cell clone by flow cytometric sorting analysis and also they studied on B-cell receptor gene rearrangement on each population by the next-generation sequencing technology after separated on a case of coexistence of HCL and CL. Their results showed that the HCL clone harbored the signature *BRAF* V600E mutation and the CLL clone harbored an *RB1* (L343fs*6) mutation. So, their studies suggested that a process of independent clonal development of multiple neoplastic B-cell populations in composite lymphoma, likely occurring somewhere after the common lymphoid progenitor stage [11].

Coexistence of CLL with MM

MM is a type of cancer from plasma cells, so MM is also known as plasma cell myeloma.

CLL and MM are different chronic lymphocytic proliferative malignancies originating from different maturation stages of B-cells. There were many reports and studies in the coexistence of CLL with MM within the same patient but the conclusion of CLL and MM on their cell clone origin is still controversial.

Studied an elderly male patient with co-existence of CLL and MM and their results showed both CLL and MM originated from the same B-cell progenitor by studying immunoglobulin gene rearrangement from peripheral blood and bone marrow with the suggestion that the coexistence of CLL with MM within the same patient was from the single clonal origin with biphenotypic concomitant [12].

Result from another group suggested that in some circumstances CLL leukemic B cells may reach a more mature state, leading to the occurrence of clinical MM [13]. Merdin group's study on s old male patient of coexistence CLL and MM suggested that clonal association in the coexistence if CLL and MM is still controversial [14].

Kough group reported two elderly cases of CLL developed to MM one case after 6 years and another case after 16 years these two patients were treated with chlorambucil, CLL response well but MM remain clinically indicating the presence of different clone origins [15]. Similar cases war reported on an elderly male patient of the coexistence of CLL and MM with the deletion of chromosome 11q22.3. 5 years later was treated with chlorambuci and dexamethasone, patient developed to MM with complex chromosomal abnormalities. Translocation of chromosomal 11 and 14 detected by FISH indicating that CLL and MM were not from the same clone involved [16]. Interestingly case reported by Pantic group with the same chromosomal abnormality -deletion of chromosome 11q22.3 as well [17].

Two cases with the concomitant CLL and MM were reported. In one patient, trisomy 12 and deletion of chromosome 14 q21q32 were detected in lymphoid cells, but not in MM cells. In another patient, no clonal abnormalities were detected by conventional cytogenetics but a deletion of chromosome 8q24 was detected by FISH technique. So, they concluded the existence of two clonally distinct B-cell malignancies at different maturation stage in both patients [18].

Brouet reported 11 cases of coexistence of CLL and MM. CLL occurred before MM in six cases and both diseases were diagnosed simultaneously in five. Results they obtained indicated the coexistence of two distinct clonal proliferations [19].

Coexistence of CLL with myeloid hematological malignancies within the same patient

The coexistence of CLL with several types of myeloid hematological malignancies including MPN and AML have been reported and studied.

Coexistence of CLL with MPN

MPN is a group of myeloid malignancies. Essential Thrombocythemia (ET), Polycythemia Vera (PV), Primary Myelofibrosis (PMF) and CML have been classified as MPN by World Health Organisation (WHO) in 2016 [20]. Studies showed all these types of MPN mentioned above are associated with CLL.

Coexistence of CLL with ET

ET is a rare type of chronic myeloproliferative malignancy characterised by the overproduction of platelets released by megakaryocytes in the bone marrow.

Patient developed ET after 10 years history of CLL and also with a history of prior exposure to Asbestos. JACK2 mutation was negative. Treated with Anagrelide [21].

Zielinska group reported an elderly male patient of coexistence of CLL and ET based on evidences from the clinical presentations, cell morphology, immune-phenotype, cytogenetics and molecular findings. The deletion of chromosome 13q, but not tp53, no mutation of JACK2 V617F were detected by FISH. Patient was treated with Immunoglobulins, Prednisone and Hydroxyurea and got ET remission and then without further treatment [22].

In another similar case report described two cases (one male and one female) of CLL with negative Philadelphia chromosome but positive with JAK2 V617F [23].

Coexistence of CLL and PMF

PMF is a type of chronic myeloid malignancy featured with occupation of fibrosis in marrow cavity resulting in a lack of production of normal blood cells.

Burgstaller., *et al*. reported an elderly female patient of the coexistence of CLL and PMF. Patient was treated with Lenalidomide and received remission in both CLL and PMF clinically [24,25].

Another group reported 8 cases of coexistence of CLL and PMF and they made 3 hypotheses: 1) a bilineage manifestation of a pluripotent stem cell proliferation, 2) independent proliferations of two distinct cell lines under a common leukemogenic stimulus or 3) an accidental association [26].

Coexistence of CLL with PV

PV is type of chronic malignancy characterised with over production of red blood cell.

There were some literature reports on the coexistence of CLL and PV [27-29].

Reported a case of coexistence of CLL and PV and studied the *JAK2V617F* and *P53H179L/P53R209fs* mutations by the targeted next generation sequencing after B lymphocytes and neutrophils were separated. They identified the *JAK2V617F* mutations in neutrophil's compartment and *P53* mutations in B lymphocytes. These results indicated that CLL and PV are independent clonal diseases in this case, rather than phenotypes derived from one clone [30].

A large retrospective analysis on 46 elderly cases of CLL/MPN (30 males and 18 females) was performed by an Italian group including 18 cases of ET, 10 cases of PV, 9 cases of CML, 6 cases of PMF, and 3 cases of MPN/myelodysplastic syndrome (MDS). They found that 1of

46 was a familial CLL and also their results showed that MPN therapy did not interfere the prognosis of patients with CLL after followed up for 49 months [31].

Coexistence of CLL and CML

CLL and CML are two different types of hematological malignancies commonly occurs in elderly population.

CML is the most common type of chronic myeloproliferative disorder, characterised with Philadelphia chromosome (Ph) in cytogenetic level and with fusion of BCR-ABL gene in molecular level.

There were some reports in three conditions in the coexistence of CLL and CML or sequential occurrence of two diseases within the same patient; 1) CML first and then CLL followed, 2) CLL first and then CML followed and 3) Co-occurrence of CLL and CML.

CML first and then CLL followed

Kumar., *et al*. reported a case, diagnosed as CML first and CLL developed after 8 month diagnosed as CML [32].

Another group reported an elderly male patient who was diagnosed as CML first and then developed to CLL with chromosome translocations of 9 and 22 (Ph) and an iso-chromosome 17 after 18 months treated with hydroxyurea [33].

There was another reported of a case with CML first and then developed to CLL with rearrangement on the long arm chromosome 11 (q22.3). The blood count became normal after treated with a combination treatment of prednisone and imatinib and responded well [34].

Reported an elderly male patient diagnosed as CML with Ph positive. Patient was treated with Imatinib and remission was achieved but this patient developed to CLL after 7 years. Remission of CML was achieved and CLL in the indolent phase [35].

Esteve., *et al*. reported an elderly female patient who was diagnosed as CML first from clinical presentation to laboratory tests. The diagnosis of coexistence of CLL and CML was set after 18 months according to clinical presentation and laboratory findings. Patient was treated with hydroxyurea but died shortly afterwards. Their results suggested CLL and CML were from two different cell clone origins by studies on immunoglobulin heavy chain gene rearrangement [36].

CLL first and then CML followed

Payandeh group reported an elderly female patient diagnosed as CLL first and then developed to CML after 64 months. Signs of CML were disappeared but CLL became dominant after a few months treatment with Imatinib [37].

Gargallo group performed studies by using the techniques of FISH and RT-PCR their results showed CLL cells arose in a Ph-negative clone in their case reported indicating CLL and CML cells were from the different cell origins [38].

Wu., *et al*. reported a 60 year old male case with a history of lymphocytosis and indolent CLL was reported. However, his diagnosis and therapy changed due to the finding of three-way variant translocation. As far as we are aware, there were no previous published reports of a variant t(9;22;11) in a patient with the coexistence of CML and CLL.

This patient had never been treated for CLL the development of CML does not appear to be therapeutically induced [34]. Interestingly, since the implementation of Imatinib the patient has had a major molecular response and his previous lymphocytosis has resolved [39].

Co-occurrence of CLL and CML

Maher., *et al*. reported a case of 69 year-old male patient simultaneous occurrence of CLL and CML and then they studied the clonal origin by separated lymphocytes and myeloid cells. Their results showed that both BCR JH rearrangement were detected in the mixed cell populations but only BCR in myeloid cells and JH rearrangement in lymphocytes was detected after separation before two cell populations were separated. Their results suggested that these malignancies arose from separate stem cells by studied myeloid and lymphoid clones separated [40].

Another report from Boddu group reported two elderly female cases coexistence of CLL and CML. Their therapeutical experiences were to use concomitant treatment with dual oral targeted therapy (dasatinib and ibrutinib) was effective and well tolerated [41].

Studied the clonal origin in CML and CLL by FISH and RT-PCR on a case with CLL from CML and their results showed CD-19 (CLL marker) and BCR-ABL (CML marker) are from different clonal cells suggesting that CML and CLL cells were not from the same cell clonal origin [42].

Coexistence CLL with AML

The coexistence of CLL and AML within the same patient is very rare comparing to other types of haematological malignancies.

Yilmaz., *et al*. reported 3 elderly patients with concomitant occurrence of AML and CLL based on the bone marrow cell morphology, immunophenotype, cytogenetics and clinical presentations. No cytogenetic abnormalities were detected at the time of diagnosis. There were no exposure to cytotoxic immunosuppressive drugs and no radiation histories in these 3 patients studied. So, they hypothesised that CLL and AML were from two different diseases [43].

Another group reported am elderly male patient of AML with aberrant CD7 expression and CEBPA mutation during the course of CLL. Patient was treated with standard induction therapy for AML but failed to achieve remission. This group also reviewed 27 cases of coexistence of CLL and AML and the analysed results showed patients AML associated with CLL have poor response to chemotherapy and poor prognosis [44].

Tambaro., *et al*. retrospectively studied the outcome on 95 patients with CLL, with acute leukemia (38 cases) and MDS (57 cases) either in concurrent or subsequent to CLL. But their results could not show any correlation in survival of CLL and coexistence with AML and MDS. All cases showed poor response to treatment [45].

Another reported on an elderly male patient presented as AML with 5 years CLL history. Flow cytometric analysis showed both lymphoid and myeloid markers but no cytogenetic abnormalities were detected. Patient did not achieve remission and died 2 months later although intensive anti-biotherapies were given [46].

Wu., *et al*. reported the first case of coexistence of CLL with Acute promyelocytic Leukemia (APL) on an elderly male patient with the findings of chromosome translocations of chromosome 15 and 17, extra copy of chromosome 8 and deletion of chromosome 7q confirmed by FISH. APL remission was achieved with normal cytogenetics after treated [47].

Coexistence of CLL or HCL with lymphoma in Richter syndrome

Richter's syndrome (RT), also named as Richter transformation was first described in 1928 by Maurice Richter with the features of large-cell lymphoma with CLL/Small lymphocytic lymphoma affecting about 5% of CLL patients featured with refractory to treatment [48]. RT also transformed to myeloid leukemia rarely and with poor prognosis. The mechanism is still unkown.

The term of RT then was introduced in 1964 with more descriptions of disease nature in histology [49]. Although diffuse large B cell lymphoma is the most common histology seen in patients with RT, Hodgkin lymphoma and T cell lymphomas have also been reported less commonly [50-52].

RT is different disorder with the CLL in some aspects of the disease association but it has the similar scenario in the genetic defects such as chromosome trisomy 12, deletion of 11q23, translocation 11 and 14, mutation of p53 and so on.

CLL increase the risk of second cancer with the same patient

Studies demonstrated CLL increase the risk of developing to second solid cancers.

Manusow and Weinerman group analysed 102 cases of treated CLL in the period from 1955 to 1974 retrospectively for the age and sex matched population. They found the risk of to develop cancer in patients with CLL was threefold, eightfold for skin cancer and twofold for other cancers [53].

From an analysis on long term and large number of samples of CLL, demonstrated the trends that CLL increased the risk of secondary primary cancers, the cancer risk was even higher in the treatment group with chemotherapies comparing to the group without treatment [54].

The strong evidence of CLL increase the second cancers with in the same patient were from the studies by Travis group on the retrospective analyses on 9456 patients with CLL from the period between 1973 to1988 and their results showed patients with CLL have significantly increased risk of developing to second cancers of lung, brain, intraocular melanoma, malignant melanoma and Hodgkin's disease compared with the general population [55].

Conclusion

CLL is a chronic lymphocytic proliferative malignancy commonly in elderly in Western world. The phenomena of coexistence of CLL with most of the other types of haematological malignancies (except ALL) within the same patient has been becoming the evident. Studies on large sample demonstrated the risk of secondary cancer is higher associated CLL.

Such complex phenomenon requires proper diagnosis, differential diagnosis and proper therapeutical strategies under the condition of the disease cause unknown.

Knowledge obtained from the studies of haematopoiesis increased the understanding in blood cell lineage in normal and pathological conditions. Clonal evolution could be one of the mechanism in the disease pathogenesis.

There are several possibilities about the coexistence of CLL with haematological malignancies within the same patient regarding the clonal origins; Co-incidence, treatment related or clonal evolution. Evidence obtained from studies suggested that the coexistence of CLL with other types of haematological malignancies within the same patient due to unrelated or co-incidence is unlikely. The treatment strategy for CLL is watch and wait. Most cases with CLL reviewed were untreated. So, coexistence of CLL due to treatment is unlikely. A simultaneous proliferation of two cell lines triggered by a single cause could an explanation but the conclusion is still controversial so far. Interactions of cancer genes in CLL with other cancer genes, genomic variation, deficiency/loss of cancer suppressor genes and even through germ line mutation process to increase the disease susceptibility could be the factors in in such complex diseases.

More cases and more molecular studies for such association of CLL with other types of haematological malignancies are needed for further studies and by the genomic sequence technology and precision medicine will help to care such patients.

This literature review has focused on the association of CLL with all types of haematological malignancies and some types of solid cancers as the cause.

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