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Investigation of Secondary Acute Lymphoblastic Leukemia (sALL) Among Acute Lymphoblastic Leukemia (ALL) Iraqi Patients

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Abstract

Acute lymphoblastic leukemia which developed after first primary solid organ malignancy (1M) considered as secondary acute lymphoblastic leukemia (sALL) and it is rare. The observational study that researches for(sALL) in worldwide and even in Iraq is limited. This study investigated (sALL) among 50 (ALL) Iraqi patients (30 children; 20 adults). Five (4 female;1 male) out of 50 (ALL) patients (10%) were with(sALL) .They asked through questionnaire form about their age , 1M , latency period and immunophenotype .They were in 14-40 years age group and with previous malignancies breast , ovary, lung and thyroid cancers. The median latency period (from 1M to sALL) was 30 months. Four of (sALL) were with B cell immunophenotype , while one was with T cell. This observational study gives an evidence of the present of (sALL) among (ALL) Iraqi patients after 1M in the adults . Since it is the first time to address the idea of this review article and has not been addressed previously, there is a need for a wide approach on this group of (sALL) patients, including surveillance epidemiology , molecular and cytogenetic study.

Keywords: ALL ,sALL , 1M , latency period , immunophenotype.

التحري عن الاصابة بسرطان الدم الليمفاوي الحاد الثانوي بين المرضى العراقيين المصابين بابيضاض الدم الليمفاوي الحاد

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الخلاصة

سرطان الدم الليمفاوي الحاد الذي يتطور بعد الورم الخبيث الأساسي الاولي (1M) يعتبر سرطان دم ليمفاوي حاد ثانوي (sALL) ويكون نادر الحدوث. الدراسات المبنية على المشاهدة التي تبحث عن سرطان الدم الليمفاوي الحاد الثانوي في جميع أنحاء العالم وحتى في العراق محدودة. تقوم هذه الدراسة بالتقصي عن سرطان الدم الليمفاوي الحاد الثانوي بين 50 حالة من المرضى العراقيين المصابين بسرطان الدم الليمفاوي الحاد (30 طفلاً ، 20 بالغ) . خمسة (4 اناث ، 1 ذكور) من أصل 50 مريض عراقي بسرطان الدم الليمفاوي الحاد (10 ٪) كانوا مصابين بسرطان الدم الليمفاوي الحاد الثانوي. تم سؤالهم من خلال استمارة استبيان عن عمرهم ، نوع الورم الخبيث الأساسي الاولي ، فترة الكمون و النمط الظاهري المناعي . كانوا

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ضمن الفئة العمرية 14−40 سنة وكانت الأورام السرطانية السابقة هي سرطان الثدي , المبيض ,الرئة و الغدة الدرقية . فترة الكمون (الفترة من الورم الخبيث الأساسي الاولي إلى ظهور سرطان الدم الليمفاوي الحاد الثانوي) كانت 30 شهرًا. أربعة من المرضى المصابين بسرطان الدم الليمفاوي الحاد الثانوي كانوا يحملون النمط المناعي الظاهري للخلية البائية ، في حين كان واحد منهم يحمل النمط المناعي الظاهري للخلايا التائية. هذه الدراسات المبنية على المشاهدة تعطي دليلا على وجود سرطان الدم الليمفاوي الحاد الثانوي بين المرضى العراقيين البالغين و المصابين بسرطان الدم الليمفاوي الحاد بعد الورم الخبيث الأساسي الاولي. وبما انها المرة الاولى لتناول فكرة المقالة الاستعراضية هذه ولم يتم تناولها سابقا، فان هناك حاجة إلى دراسة واسعة حول هذه المجموعة من المرضى العراقيين المصابين بسرطان الدم الليمفاوي الحاد الثانوي بما في ذلك الدراسة الوبائية ,الجزيئية والوراثية الخلوية للمرض.

Introduction

Cancer metastasis is a process in which cancer cells travel from the primary cancer site by lymph system or bloodstream to a different sites of the body, settle and grow in this new site . Cancer that formed from cells that have spread is called secondary cancer [1]. During this process, cancer cells go through four steps including detachment from a primary cancer site, migration through lymph or blood stream, invasion the new site and adhesion [2]. The microenvironment of cancer (such as growth factors, chemokines), vascularization, provide special cytokines play important role in making many changes in growth factor signaling, cell-cell adhesion, gene expression (various oncogenes, tumor suppressor genes and metastasis suppressor genes are known to affect the invasiveness and the metastatic potential of tumor cells) and motility or cell shape, that due to cancer metastasis [3]. The main threat and the reason for most cancer deaths are not primary cancer but the secondary one, it is responsible for 90% of cancer deaths [4].

Acute lymphoblastic leukemia (also known as Acute Lymphocytic Leukemia) is a malignant disease caused by the genetic alterations of the lymphocyte precursor cells of the bone marrow. While, secondary acute lymphoblastic leukemia (sALL), defined as (ALL) following another malignancy, irrespective of whether patients received prior therapy. Secondary acute lymphoblastic leukemia considered as a rare disease [5]. The therapy-related to acute myeloid leukemia (AML) , or secondary AML is well recognized and entity accepted by the World and Health Organization (WHO), while therapy related to (sALL) is not , mostly due to the rarity of this disorder [6].

Single or cluster of cancer cells (cancer stem cells) which have ability to self-renew and eventually form diverse tumor cell population, separate from primary cancer site travel by lymph system or bloodstream to bone marrow that contain hematopoietic cells ,settle and grow ,then effect on hematopoietic stem cells and increased there differentiation and proliferation . Bone marrow is a major target organ for metastasis, evidently providing a fertile soil for disseminated tumor cells [7].

Prior exposure to chemotherapy or radiotherapy has been postulated as a possible independent risk factor for the development of (sALL) and therefore there is a possible association with poor prognosis [8]. Rosenberg *et al.*(2017)[9] revealed that patients who took a treatment of a prior malignancy (chemotherapy and radiation) were associated with a higher incidence of ALL among cancer survivors and a higher risk of death after (sALL). Therapy-related (ALL) is divided into main types: alkylating agent/radiotherapy–related, caused by complete or partial deletion of chromosome 5 or 7, and topoisomerase II inhibitor–related , which caused *MLL* gene rearrangement that is one of the most factors that increase the risk of (sALL) [10]. Immunodeficiency in the form of either malignancy, antineoplastic treatment, autoimmune disorders, and immunomodulation have also been described as risk factors for the development of lymphoblastic leukemia [8]. As well as there are some of cytogenetic abnormalities associated with occurrence of (ALL) as a secondary cancer such as, rearrangements of the *MLL* gene on chromosome 11 appear more common among (sALL) patients with prior malignancies compared with de novo (ALL), supporting the argument that secondary ALL (sALL) is a distinct entity and may be linked to specific therapies [9]. The chromosomal 11q23 abnormality is the most common cytogenetic alteration in secondary acute lymphoblastic leukemia [11].

Immunophenotyping by means of multi-channel flow cytometry (MFC) has become the standard procedure for ALL diagnosis and subclassification, about immunophenotype of B-cell ALL, the most

important markers for diagnosis and subclassification of B-cell ALL are CD10,CD19, CD20, CD22, and CD79a ,TdT. The earliest B-lineage markers are CD19, CD22 (membrane and cytoplasm) and CD79a, a positive reaction for any two of these three markers, without further differentiation markers, identifies pro-B ALL (B-I subtype) .The presence of CD10 antigen (CALLA) defines the "common" ALL subgroup (B-II subtype). Cases with additional identification of cytoplasmic heavy mu chain constitute the pre-B group (B-III subtype) , whereas the presence of surface immunoglobulin light chains defines mature B-ALL (B-IV subtype). While, the markers that used in immunophenotyping of T-cell ALL are CD1a, CD2, CD3 (membrane and cytoplasm), CD4, CD5, CD7 and CD8. CD2, CD5 and CD7 antigens are markers of the most immature T-cells, but none of them is absolutely lineage-specific, so that the unequivocal diagnosis of T-ALL rests on the demonstration of surface/cytoplasmic CD3. Recognized T-ALL subsets are the following: pro-T EGIL T-I (cCD3+, CD7+), pre-T EGIL T-II (cCD3+, CD7+ and CD5/CD2+), cortical T EGIL T-III (cCD3+, Cd1a+, sCD3+/−) and mature-T EGIL T-IV (cCD3+, sCD3+, CD1a−).A novel subgroup that was recently characterized is represented by the so called ETP-ALL (Early-T Precursor), which shows characteristic immunophenotypic features, namely lack of CD1a and CD8 expression, weak CD5 expression, and expression of at least one myeloid and/or stem cell marker [12]. Finally, the consensus by European Group for the immunological characterization of leukaemias (EGIL) is that a threshold of 20% should be used to define a positive reaction of blast cells to a given monoclonal antibody, except for CD3, CD79a and TdT, which are considered positive at the 10% level of expression[13].

This study aimed to investigate the factors related to (sALL) occurrence.

Methods

Patients/Study Population

Fifty Iraqi patients ; 30 cases were children (1-14 years) who were admitted to the Central Teaching Hospital of Paediatric ,and 20 cases were adults(15-40 years, more than 40) who were admitted to the Baghdad Teaching Hospital were clinically diagnosed with (ALL) by the consultant medical staff of the hospitals. They informed about the goal of this study and requested to fill the questionnaire form. They were divided into two groups, as having primary (ALL) or they were with (sALL). Those who were with (sALL) enquired of their 1M, latency period (from 1M to s ALL) and immunophenotype. CD19, CD20, CD22, CD10 and CD79a were the markers used for diagnosis and subclassification of B-cell ALL. While, the markers used for diagnosis and subclassification of T-cell ALL were CD1a, CD2, CD3, CD4, CD5, CD7 and CD8.

Results and Discussion

Five cases out of 50 (ALL) Iraqi patients (10%) were with (sALL).The demographic characteristics of (sALL) patients are shown in Table-1.

As shown in Table-1 females were higher than males with (sALL) (80%). This result is in agreement with other studies conducted by Swaika (2017)[8] and Rosenberg (2017)[9] who revealed that females with (sALL) represent a higher percentage than males , also they found that females with (sALL) is higher than those with de novo ALL. This indicates that (sALL) is most pronounced in females than males.

According to age group all (sALL) patients in this study were limited in 14-40 year age group , that's may be related to that the children and old age groups patients with (sALL) do not have the ability to resist secondary cancer and survive longer because of their low level of immunity. Thus , many studies demonstrated that (sALL) was associated with a significantly lower survival as compared to de novo (ALL) (6–15 months) [8,9]. As well as Rosenberg *et al*.(2017) [9] who reported that (sALL) was more pronounced among <40 years old patients . According to primary tumor , it not surprising that this study shows that breast cancer represents the higher ratio among s (sALL) patients ,that's because it is the common cancer in females as announced by the latest Iraqi Cancer board registration for 2012 [14].

Additionally, most of the cases were females, so the breast cancer occur more than other types of cancers. Also, it was the highest percentage among other primary cancers in many previous studies [8, 9].

Table 1-The Criteria of (sALL) in Iraqi Patients

Patients Characteristics	Number of (sALL) Patients	%
Gender		
Male Female	1 4	20 80
Age		
1-14 14-40 More than 40	----- 5 -----	100
Primary Tumors		
Breast Lung Thyroid Ovary	2 1 1 1	40 20 20 20
Latency Period		
<2 years 2-5 years	2 3	40 60

In addition to breast cancer, lung, thyroid and ovary cancers have been proved to be the most cancers that have the predisposition to develop (sALL) [8]. Indeed , breast cancer is one of common cancer that are particularly well known to metastasize to bone marrow that is a target organ for metastasis and provide a fertile soil for disseminated tumor cells and various cell types, the marrow contain osteoblasts , endothelial cells, nerve cells, adipocytes, CXCL12-abundant reticular (CAR) cells and mesenchymal stem cells collectively serve as a specific 'niche' for hematopoietic stem cells (HSCs), maintaining the functions of HSCs including homing, self-renewal, quiescence and differentiation, it is now known that malignant cells that disseminate to and develop in the bone marrow do so by hijacking the bone marrow niche, in fact, breast cancer is home to the marrow using mechanisms similar to HSC homing Not only are the disseminated tumor cells supported by their chosen niche, but they can also instigate niche changes that preferentially cater to malignant cells[15].

Latency period was defined as the interval time between primary cancer and (sALL) . The high percentage of (sALL) patients in the present study were with a latency period of 2-5 years. However, Swaika (2017) [8] illustrated that the latency period is variable according to the 1M, where patients with a previous history of lymphoma and/or previous primary leukemia and lung malignancies had the shortest latency period, whereas patients with previous ovarian or thyroid cancer had the longest interval, possibly reflecting the natural history of the underlying 1M.

Table 2-Immunophenotype of Patients with Secondary Acute Lymphoblastic Leukemia

No.	Immunophenotype	Positive markers	Negative markers	Immunophenotypic subgroups
1	B-cell	CD19(85%), TdT (40%), CD79a (40%)	CD10, CD20, CD22, CD1a, CD2, CD3, CD4, CD5, CD7, CD8	Pro-B ALL
2	B-cell	CD79a(94%),CD20(87 %), CD10(28%), CD19 (57%)	CD22, CD1a, CD2, CD3, CD4, CD5, CD7, CD8, TdT	Pre-B ALL (CALLA Positive)
3	B-cell	CD79a(37%), CD10 and CD19(82%), TdT(28%)	CD20, CD22, CD1a, CD2, CD3, CD4, CD5, CD7, CD8	Pre-B ALL (CALLA Positive)
4	B-cell	CD79a(25%), CD10 and CD19(89%), TdT(13%)	CD20, CD22, CD1a, CD2, CD3, CD5, CD4, CD7, CD8	Pre-B ALL (CALLA Positive)
5	T-cell	CD2(85%),CD7(80%) CD5(45%),CD3(75%)	CD4, CD8, CD1a, CD10, CD19, CD20, CD22, CD79a, TdT	Pre-T ALL

About immunophenotyping B cell (sALL) was highest than T cell and this may be due to that the majority of (ALL) patients have B cell immunophenotype [16-19]. Shivakumar *et al*.(2008)[5] noted that most (sALL) patients at 18-59 age group had high prevalence of B cell immunophenotype .

As the idea of this Review article is the first to time to be taken , Further prospective researches are needed to detect the most clinical and genetic higher risk factors that contribute in (sALL) developing among Iraqi patients providing a screening and prevention strategies for this rare and adverse type of leukemia.

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