Secondary Acute Lymphoblastic Leukemia after Hodgkin’s Lymphoma or a Coincidental Association of Two Hematological Malignancies?

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ABSTRACT

Secondary acute lymphoblastic leukaemia (sALL), defined as acute lymphoblastic leukaemia following another malignancy, irrespective of previous treatment, is a rare disease, and its biological characteristics have not been accurately described. We report the case of a 24-year old patient followed for Hodgkin’s lymphoma at our clinic, who develops and is diagnosed, less than a year after obtaining complete remission, as having pro-B acute lymphoblastic leukaemia. This case has been a real diagnostic and treatment challenge, as sALL following another haematological malignancy is quite rare. Conclusion: It is necessary to better identify the prognostic factors of haematological malignancies in order to prevent the appearance of sALL.

Keywords: secondary acute leukaemia, Hodgkin’s lymphoma, immunophenotyping, 11q23 mutation, alkilating agents, prognostic factors

INTRODUCTION

Secondary acute lymphoblastic leukaemia (sALL), defined as acute lymphoblastic leukaemia following another malignancy, irrespective of previous treatment or not, is a rare disease (1). While acute myeloid leukaemia secondary to treatment is a well-known entity, accepted by the WHO classification, sALL following cytostatic treatment, is not mostly due to the fact that it is quite rare (2).

Most literature reported sALL’s are case reports or case-series and there is no comprehensive large-scale analysis (1). As to the onset and evolution characteristics of sALL different papers report an average time period of 8.3 years in order to develop a secondary malignancy (without excluding leukaemia) following the Hodgkin’s lymphoma. A shorter time period was described in sAML cases associating the 11q23 mutation, but not for sALL. Similarly, a considerable latent period has been associated to the presence of the
complex karyotype, especially mutations involving chromosomes 5 and/or 7 or parts of them. This is the case with sAML, but not with sALL (3). T cell ALL is more frequent in patients <18 years old than in those over 18. There is no significant correlation between age and Burkitt sub-type, cytogenetic mutations of 11q23, t(9;22) and the normal or complex karyotype (4). However, one should be aware that 11q23 mutations are more often detected than other mutations (5). Radiotherapy rather than chemotherapy seems to be a determinant of sALL. With respect to chemotherapy, it should be noted that most patients (94%) with sALL and 11q23 mutations have been previously treated with topoisomerase II inhibitors. This is similar to sAML with associated 11q23 mutations (6). The rate of complete remissions is very low, and it is higher with older ALL patients (6).

There are two pathogenic mechanisms involved in the development of this type of secondary acute leukemia: the existence of two malignant cell clones at the time of the initial diagnosis, one of them being destroyed by chemotherapy, allowing the development of the other one; the development of leukemia at a less differentiated stage of the stem cell (7). The time period to the appearance of sALL (so called latency period) is significantly longer for patients with sALL that present a complex karyotype than for patients with other mutations (1).

Having compared the evolution of sALL patients according to cytogenetic groups, Medical Research Council/Eastern Cooperative Oncology Group ALL trial showed that 5 years survival rate was zero in patients with 11q23 mutations, as compared to a 24% and 33% survival rate for patients with t(4;11) and other aberrations of 11q23 (6).

This modest evolution for sALL patients is similar to the one reported in the case of sAML patients (2). This is why we should identify the prognostic factors, especially biomarkers that can predict the evolution of sALL for malignancy presenting patients in order to prevent this disease (7).

The poor evolution of these patients, irrespective of treatment, emphasizes the need for a better understanding of the molecular and genetic background of this disease. This can pertain to the genetic polymorphism of the detoxifying enzymes, such as NAD(P)H: quinone oxidoreductase, glutathione S-transferases, and cytochrome P450 CYP3A; the polymorphism of these genes has been proven to be directly connected with the occurrence of secondary leukemia (9).

Another variable could be the appearance of germ line mutations at the level of the ATM gene (ataxia-telangiectasia mutated) that has been specifically associated with T cell ALL (8).

Following the analysis of these genes other pathogenic events can be discovered in sALL.

CASE REPORT

We present the case of a 24-year old female patient without any significant familial history, without prior exposure to toxic substances, previously followed at our clinic for Hodgkin’s lymphoma, nodular sclerosis subtype, type I BNLI, stage IIBb (at time of initial diagnosis).

The onset of disease dates from august 2010 and consisted of the appearance of a right-sided subclavian tumour of about 4 cm in diameter, accompanied by general signs (weight loss, fever, profuse sweating). A ganglion biopsy was carried out followed by the hystopathologic and immunohistochemical examinations.

The initial thoracic CT scan showed: Adenopathy of 3.6 cm in the right-side supraclavicular fossa, with a mass effect on the subclavian artery, the jugular vein and the common carotid artery. Adenopathy of 1.6 cm in the left-side supraclavicular fossa. Multiple pre-vascular anterior mediastinal adenopathies (sized between 0.9 cm and 2.6 cm), some of them grouped in a block of 4.6 cm. In the cranial part, the adenopathic block compresses the left-side brachiocephalic venous trunk, completely surrounding it in its lateral segment. No intrapulmonary localised lesions. Conclusions: bilateral mediastinum and supraclavicular adenopathies. Initial bone marrow biopsy: no bone marrow invasion. Lab examinations showed an increased erithocyte sedimentation rate (ESR), and lactic dehydrogenase (LDH). It was concluded that she was in stage IIib of Hodgkin’s lymphoma.

We performed chemotherapy consisting of 3 cycles of ABVD type therapy with unsatisfactory results. Thus, we decided to continue with BEACOPP type therapy. After 2 such cycles, the patient achieved complete remission that was further confirmed by PET-CT examination.
Thereafter, the patient came frequently for regular re-evaluations that confirmed maintenance of the complete remission.

In June 2011, the patient presented again to our clinic with latero-cervical micropolyadenopathies of 1-1.5 cm and fever. She did not have liver or spleen enlargement or other symptoms. The CBC showed a normal level of haemoglobin (Hb) (12.5g/dL), leucocytosis (34,300/mm³) with lymphocytosis (75%) (see Figure 1), normal platelets count (231,000/cumm), ESR=15mm/h, while the blood biochemistry showed: aminotransferases, GGT, alkaline phosphatase, uric acid, C reactive protein within normal range and an increased LDH level (773U/L). We than performed the abdominal ultrasound and the thoracic X-ray which were both normal.

**Preliminary discussion**

At this point in time, the differential diagnosis was to be made between recurrence of the Hodgkin’s lymphoma, non Hodgkin’s lymphoma with blastic discharge, infectious mononucleosis, acute lymphoblastic leukemia, lymphoid blastic crisis type onset of chronic granulocytic leukemia, CLL, prolymphocytic leukemia, LGLL, autoimmune diseases, or viral or bacterial infections (A hepatitis, brucellosis, tuberculosis). Thus, we recommended viral serology tests for infections with the Epstein Barr virus, CMV, Toxoplasmosis, HVA, HVB, HVC which turned out to be all negative. The next step was to perform an immunophenotyping of the lymphocytes from the peripheral blood. The analysis was performed using the BeckmanCoulter FC500 cytometer, and the CXP Software. The technique used was the erythroylisis without washing. The gating strategy was the expression of CD45/SS and FS/SS (Figure 2).

At this point in time, our diagnosis was: Leukocytosis with reactive lymphocytosis in the context of an acute viral infection (possibly during seroconversion); Hodgkin’s lymphoma nodular sclerosis pathologic subtype, type I BNLI, stage II Bb at diagnosis – now in complete remission.

Two weeks later, the patient returns to our hospital with the same clinical picture. This time, the CBC showed: moderate anaemia (Hg=9.2d/dL), higher leucocytosis (96,700/mm³), moderate thrombocytopenia (53,000/mm³), biological inflammatory syndrome (VSH=32mm/h), while the peripheric blood sample showed 80% of lymphoblasts.
Biochemistry showed an increasing LDH as to the previous evaluation (889 U/L), C reactive protein rising as well (1.6 mg/dl), aminotransferases, alkaline phosphatase, GGT within normal range. Bone marrow examination showed a hypercellular hematogenic marrow due to lymphoid infiltration, with approximately 88% small blastic cells with a tachychromatic, round, regular nucleus, extremely reduced cytoplasm, rare mature or intermediate neutrophils, extremely rare non-thrombogenic megakaryocytes.

The abdominal ultrasound exam did not show any abnormal elements. We discussed the possibility of performing a lumbar puncture in order to assess the expansion of the disease, but it was postponed due to the increased number of blastic cells in the peripheral blood.

The immunophenotyping of 166,320 bone marrow cells/mcl, identified a CD45 population of 90%, out of which 92.5% blasts, 3% lymphocytes, 2% granulocytes, 1% monocytes. In the blasts area intracytoplasmatic CD79a+ 90%, CD34+ 8%, CD117+ 10%, CD38+ 99%, CD9+ 99%, HLA-DR+ 100%. Conclusion: majority of pro-B lymphoid population (Figure 3).

Further investigations included the cytogenetic test that showed the absence of Philadelphia chromosome, the existence of t (4;11), which is more frequent among children (80%), (the MLL gene of 11q23 merges with the AF4 gene of 4q21 that can be detected through PCR) and the molecular test that showed the existence of the MLL mutation (rearrangement of the 11q23 area) (see Figure 4).

**Final diagnosis**

Philadelphia negative precursor B cell lymphoblastic leukemia with pro-B lymphoblast leukemia, with the presence of the MLL-AF4 mutation and t (4;11) (25);

Hodgkin’s lymphoma nodular sclerosis pathologic subtype type I BNLI stage IIBb at diagnosis – now in complete remission.

**Therapy and evolution**

Medical treatment started with the pre-induction phase with dexamethasone which caused leukocytes to decrease quickly in 3-4 days to 2,400/mmc, and continued with the international protocol “ALL trial MRC UKALL XII/ECOG E2993”. Thus, we performed a first cycle of induction of complete remission (preliminary stage + stage I + stage II) in July 2011, and the patient achieved complete remission after the first 4 weeks. We did the prophylaxis of CNS involvement by means of intra-thecal administrations of cytostatics. Taking into account the existing negative prognostic factors, the patient received a “consolidation” regimen with high dose cytarabine and mitoxantrone followed by an allograft transplantation at the first complete remission. Two such “consolidation” regimens were performed. The patient was referred for allograft transplantation of hematopoietic stem cells, which took place in February 2012. The consequent evolution was...
favourable, and the donor’s marrow is functional at present.

It is noteworthy that the patient evolution under treatment was quite problematic: severe aplasia, which continued for a long time (even following the initial corticotherapy) and determined us to postpone the administration of cytostatics as compared to the protocol. There were also severe thrombocytopenias that forced us to postpone the intra-thecal administrations of cytostatics. The patient also presented numerous complications following the transplant, but at present, the donor’s marrow is completely functional.

DISCUSSIONS

We were particularly interested in the association of the two haematological malignancies (Hodgkin’s lymphoma and ALL) within a very short period of time following the complete remission of the first one, that is 6 months. We must also highlight the fact that we did not use aggressive chemotherapy. The patient underwent only 3 ABVD type polychemotherapy cycles and 2 BEACOPP type cycles, after which she achieved complete remission.

The most commonly reported associations are those between solid tumours and Hodgkin’s lymphoma, with pulmonary, mammary, colon, stomach, urinary bladder, ENT, thyroid gland, esophagus, liver, pancreas, melanoma and sarcomas being the most frequently reported ones (1). Among the haematological malignancies that occur following treatment of Hodgkin’s lymphoma, non-lymphoblastic leukaemia, non-Hodgkin’s lymphoma, myelodysplastic syndrome, AML are the most common ones (8,10-13). It seems that the risk of developing these associations depends greatly on the therapeutic strategy and certain prognostic factors in relation to the patient. Radiotherapy used alone is associated to a lower risk, combined chemotherapy using alkylating agents (MOPP, BEACOPP) plus radiotherapy is associated to the highest risk, and poly-chemotherapy alone has a moderate risk. Radiotherapy and the alkylating agents are carcinogens and that is why we should study secondary malignancies following such a treatment in order to prevent them. The patient’s age at the time of treatment for Hodgkin’s lymphoma can also significantly influence the risk of a secondary malignancy. Although the absolute risk is higher with older patients, the relative risk of developing secondary malignancies is higher with younger patients (14-17).

Since the use of alkylating agents increases the risk of a secondary leukaemia and radiotherapy contributes to the appearance of other malignancies, future therapy protocols should take into consideration reducing serious side effects, maintaining the survival rate. It is also necessary to investigate the impact of the additional risk factors and to closely monitor the Hodgkin’s lymphoma patients throughout their entire life in order to be aware of the new signs and symptoms that the patients may present (18-21).

Other particular features of our patient include the type of leukemia (proB), which is quite rare among adults (11%) and the presence of the t(4;11) mutation that is also more common among children.

Chromosomal translocations leading to merges of the MLL gene are common events among ALL patients and are especially common among children patients and those with secondary leukaemia. MLL merges with numerous partner genes and the identity of these partners influences the ALL prognostic with the existing 11q23 mutations (18,20,22,23). 11q23 anomalies are commonly spread in certain acute primary leukaemia of the adult and child, as well as in the majority of acute secondary leukaemia following the treatment with topoisomerase II inhibitors (etoposides, doxorubicines) (20,21). In the WHO classification, acute leukaemias with 11q23 aberrations are a distinct category of recurrent genetic aberrations (1). Large scale studies have proved that acute leukaemias with such cytogenetic anomalies have a poor prognosis (23). Recent studies have

**FIGURE 4.** Two photographs showing MLL probes (Dual Color, 5’MLL (11q23) - FITC; 3’MLL (11q23) - Texas Red) on culture plates after 24 h; mutation MLL (11q23 rearrangement region).
shown that their prognostic depends on the merging partners of 11q23 and differs among children and adults. ALL with t(4;11) (q21;q23) has a bimodal distribution of the age and represents 50% of the ALL cases among babies <6 months, 10-20% among babies >6 months, 2% among children, 7% among adults. Among adult patients with this mutation the rate of the complete response is 75%, but the prognostic is reserved, with an overall survival of 7 months (20,22,23).

The indication of the allograft transplantation with this cytogenetic anomaly is still debatable, as it is subject to many studies all over the world (17,18,20,24). However, conventional chemotherapy and the transplant of hematopoietic stem cells do not seem to be enough in order to improve the prognostic of ALL patients with associated 11q23 aberrations. The demethylating agents of the DNA, such as decitabine, as well as other agents (PRMT1, the HOX, EPHA7, PBX, GSK-3, RAS genes, thermal shock proteins – HSP 90, MCL-1, DOT1-like) are candidates for new targets in the therapy of ALL with 11q23 (19-22).

Although the patient presented many negative prognostic factors, the response to the treatment was really good, and she was able to achieve complete remission within 14 days from the beginning of the chemotherapy. Also, one should note the fact that complete remission was maintained, both for the lymphoma and for the leukaemia, and the patient was able to perform the transplantation 6 months after diagnosis of the ALL.

We should also point out the different problems that occurred during the therapy such as severe and prolonged aplasia, which were difficult to bear with, for the patient and made it necessary for us to postpone the administration of cytoxic agents as compared to the protocol. There were also severe thrombocytopenias that led to delays in the intra-thecal administrations of cytoxic agents according to the protocol.

CONCLUSIONS

In our opinion, the most interesting fact about this case report is the association of the two haematological malignancies (the Hodgkin’s lymphoma and ALL) within 6 months after achieving complete remission of the first one.

Another important fact is the probable onset of the leukemia either with leukocytosis – lymphocytosis, with no lymphoblasts in the peripheral blood or with bone marrow examination revealing an immunophenotypical profile of young cell lymphocytosis. This tableau changes in a few weeks outlining the criteria of diagnosis for ALL. The type of leukemia – proB with the presence of the t(4;11) – is a particular feature of this case, since that type is more frequent in children than in adults.

Although the patient presented many negative prognostic factors, her response to treatment was really good and we were able to achieve complete remission within the first course of induction chemotherapy. Considering the fact that this type of patients represent a therapeutic challenge and that the management of two haematological malignancies is very difficult we consider that better understanding of the pathophysiological mechanisms of secondary leukaemia and the identification of reliable prognostic factors for haematological malignancies, is of paramount importance in order to prevent the appearance of sALL.

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REFERENCES


SECONDARY ALL AFTER HODGKIN’S LYMPHOMA OR A COINCIDENTAL ASSOCIATION OF TWO HEMATOLOGICAL MALIGNANCIES?


