

A Rare t(11;17) in Secondary Acute Myeloid Leukaemia Following Treatment of Hodgkin Lymphoma: A Case Report and Literature Review

Hodgkin Lenfoma Tedavisi Sonrası Sekonder Akut Miyeloid Lösemide Nadir Bir t(11;17): Bir Olgu Sunumu ve Literatür İncelemesi

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ABSTRACT

Secondary Acute Myeloid Leukaemia (AML) is referred to as Therapy-related Acute Myeloid Leukaemia (t-AML) or AML evolving from antecedent haematological disorders and it is a rare disease. We report a case of a 40-year-old lady who developed AML after four years on multiple lines of treatment due to Refractory Hodgkin Lymphoma. She presented with progressive lethargy and pancytopenia. Bone marrow aspiration, trephine biopsy and flow cytometry immunophenotyping findings suggest Acute Myelomonocytic Leukaemia (AMML). Cytogenetic analysis showed the presence of rare t(11;17). This translocation was predominantly in AMML and Acute Monoblastic/Monocytic Leukaemia or variant type of acute promyelocytic leukemia (M3) and rarely associated with therapy-related AML.

Keywords: Therapy-related AML; Secondary AML; Hodgkin Lymphoma; t(11;17)

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ÖZET

Sekonder Akut Miyeloid Lösemi (AML), Tedaviye Bağlı Akut Miyeloid Lösemi (t-AML) veya önceki hematolojik bozukluklardan gelişen AML olarak adlandırılır ve nadir görülen bir hastalıktır. Bu yazıda, Refrakter Hodgkin Lenfoma nedeniyle birden fazla tedavi hattında dört yıl sonra AML gelişen 40 yaşında bir bayan hastayı sunuyoruz. İlerleyici uyuşukluk ve pansitopeni ile başvurdu. Kemik iliği aspirasyonu, trepan biyopsisi ve akış sitometrisi immünofenotipleme bulguları Akut Miyelomonositik Lösemi (AMML) düşündürür. Sitogenetik analiz, nadir görülen t(11;17) varlığını gösterdi. Bu translokasyon ağırlıklı olarak AMML ve Akut Monoblastik/Monositik Lösemide veya akut promyelositik löseminin (M3) varyant tipindeydi ve nadiren tedaviyle ilişkili AML ile ilişkiliydi.

Anahtar Sözcükler: Terapiye bağlı AML; İkincil AML; Hodgkin lenfoma; t(11;17)

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INTRODUCTION

Secondary AML may develop from the evolution of a particular antecedent haematologic disorder, or it may arise as a complication of prior cytotoxic chemotherapy or radiation therapy in the case of therapy-related AML (1). In the latest World Health Organization (WHO) classification system (2016); AML has many subtypes and one of them is therapy-related AML.

CASE REPORT

A 40-year-old Malay lady was diagnosed with Hodgkin Lymphoma Nodular Sclerosis Stage IVB in 2014. At that time, she presented with neck swelling and constitutional symptoms. She received multiple lines of chemotherapy, including ABVD [Adriamycin(Doxorubicin), Bleomycin, Vinblastine, Dacarbazine] for 1 cycle, ICE (Ifosfamide, Carboplatin, Etoposide) 3 cycles, GDC (Gemcitabine, Dexamethasone, Cytarabine) 5 cycles, DHAC (Dexamethasone, Cytarabine, Carboplatin) 3 cycles, AVD (Adriamycin, Vinblastine, Dacarbazine) 4 cycles, and Brentuximab due to the rapid progression of the disease and refractory towards the chemotherapies given. Four years after receiving multiple lines of salvage chemotherapies, she started to develop pancytopenia, which was persistent for more than six months despite not on any myelosuppressive chemotherapy. Subsequent bone marrow evaluation revealed a hypocellular marrow with presence of atypical cells suggestive of marrow infiltration by primary disease. Therefore, she was started on immunosuppressive therapy, which was prednisolone and followed by cyclosporin, based on the adaption strategy of using immunosuppression to overcome autoimmunity in bone marrow failure. In addition, she was supported with oral eltrombopag and pegfilgrastim injection to stabilize the platelet and leucocyte counts, respectively. Although the blood counts were partially responded to, she was not dependent on regular blood product transfusion and was free from any fatal neutropenic sepsis.

She was on weekly full blood picture monitoring and later noted to have 24% circulating blast (including promonocytes) as shown in Figure 1A. The white

Therapy-related myeloid neoplasm is a complication of primary malignancies, including solid tumors and haematological neoplasms per se or developed following the exposure to chemotherapy drugs (such as alkylating agents and DNA topoisomerase II inhibitors) or radiation (2). Chromosomal damage caused by these agents resulted in chromosomal aberration and led to leukaemogenesis (3). A translocation t(15;17)(q23;q25) was reported in therapy-related and infant AML which *SEPT9* gene as a fusion partner of *MLL* gene (4). So far, very limited cases have been reported regarding secondary AML with t(11;17).

blood cell count at that time was $3.75 \times 10^9/L$, hemoglobin of 8.8 g/dL, platelet count of $5 \times 10^9/L$ and monocytosis with the absolute count of $1.81 \times 10^3/\mu L$. Urgent bone marrow aspiration (BMA) was done, but unfortunately, it was a dry tap and only the touch imprint was submitted. The imprints showed numerous blast cells with a mixture of myeloblast, monoblasts, promonocytes and mature monocytes (Figure 1B). The trephine biopsy showed hypercellular marrow with diffuse infiltration by the blasts, as shown in Figure 2. These cells expressed CD117, MPO, CD68 (heterogenous) and CD34 (heterogenous). No Hodgkin cells and Reed-Sternberg cells were seen. Other lineages were markedly suppressed. The flow cytometry immunophenotyping from the peripheral blood (in view of failed BMA) showed two distinct populations at the blast window. About 54% of the blasts expressed CD34, CD117(heterogenous), MPO(heterogenous), CD13, CD33, HLA DR, CD64 and dim CD123. Another population accounted for 22% expressed CD13, CD33, CD117 (heterogenous), CD11b, HLA DR, CD300e (heterogenous), CD64 and CD14, most likely promonocytes. Cytogenetic analysis revealed t(11;17)(q23;q25) shown in Figure 3. However, no Fluorescence In Situ Hybridisation (FISH) was done. She had been commenced with an induction regime of AML 3+7 (Daunorubicin + Cytarabine) protocol. However, she succumbed to death while on induction chemotherapy because of the disease complication.

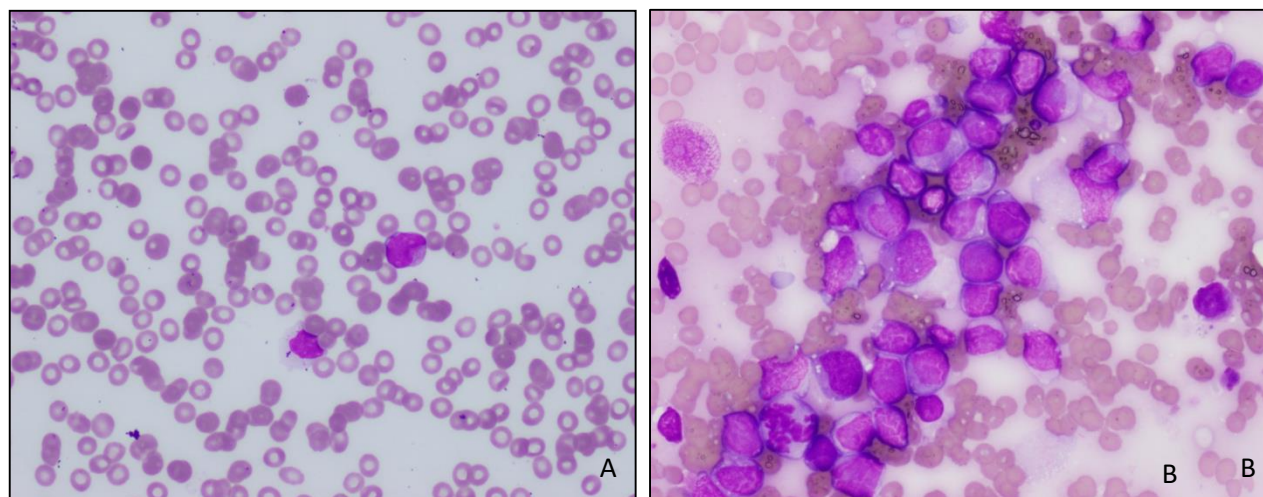


Figure 1A: Full blood picture show myeloblast. **Figure 1B:** Trephine touch imprint show numerous blast cells and monocytic lineages. [Stain: Wright Giemsa Stain (1A) and May-Grunwald Giemsa stain (1B), under 40x magnification].

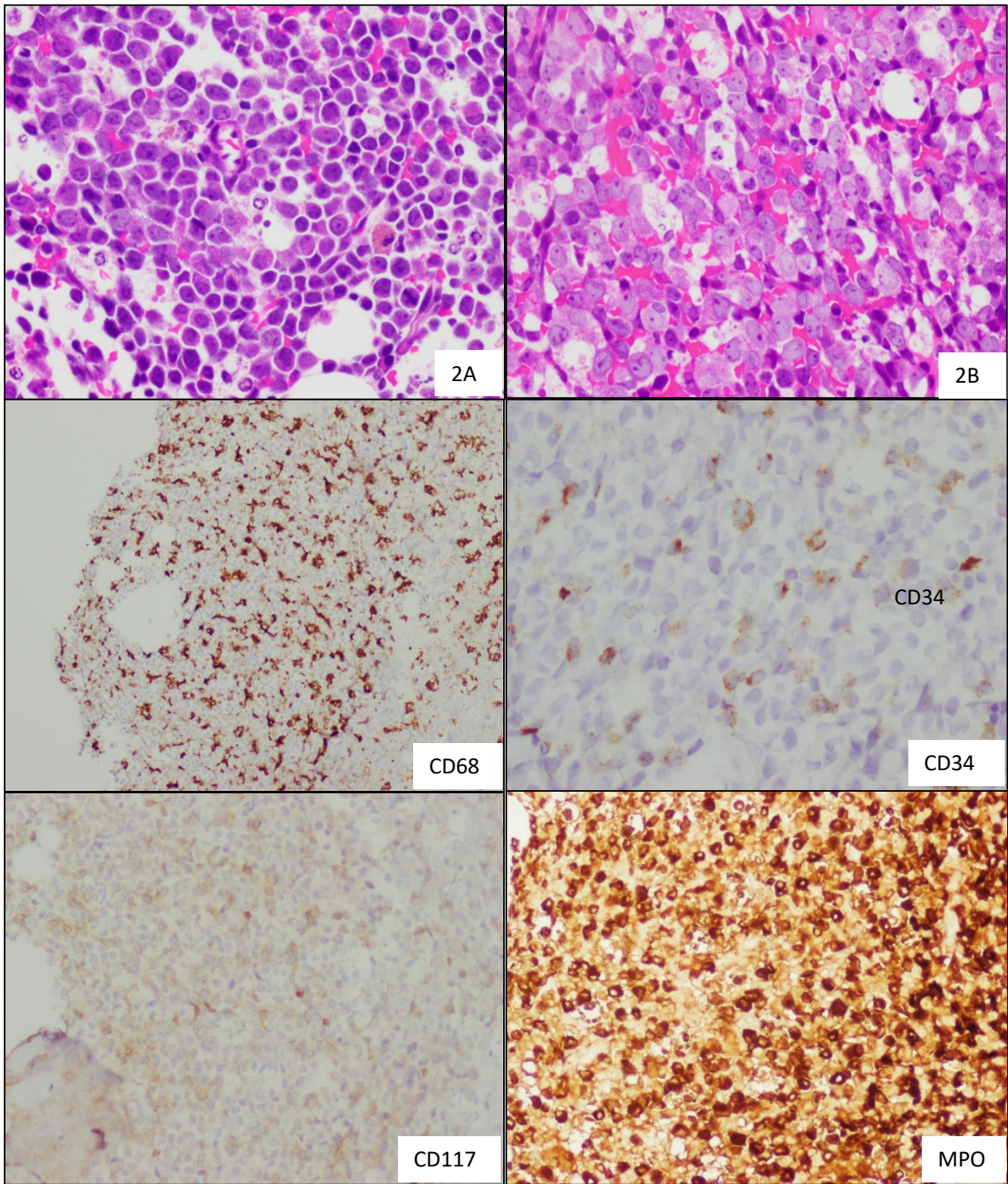


Figure 2A & 2B: Diffuse infiltration of blast cells with many histiocytes intermingled. No Reed-Sternberg cells or Hodgkin cells were seen. The blast cells expressed MPO, CD117, CD68 (heterogenous) and CD34 (heterogenous). (Stain: Hematoxylin and Eosin, under 40x magnification).

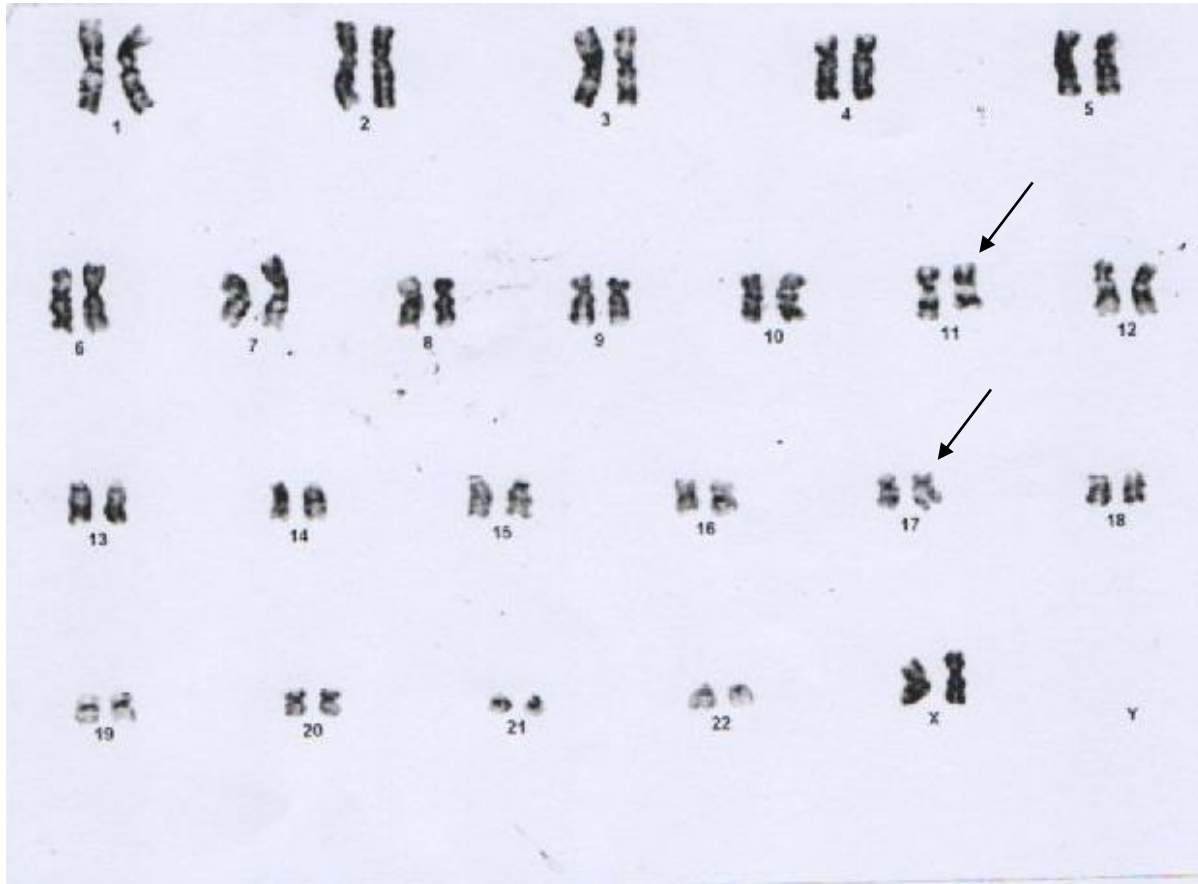


Figure 3: The karyotype of this case is as follows: 46, XX, t(11;17)(q23;q25).

DISCUSSION

Secondary AML can be classified into AML that develops due to a pre-existing myeloid malignancy and therapy-related myeloid neoplasm (t-MN). The pre-existing myeloid malignancies include myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), or MDS/MPN. In contrast, therapy-related myeloid neoplasm develops as a complication of prior cytotoxic therapy. Secondary AML account for 25–35% of all AML cases (1)(5). We made a diagnosis of therapy-related AML because she received multiple lines of cytotoxic therapy and there was no evidence of antecedent myeloid malignancy.

Hodgkin lymphoma (HL) patient who received cytotoxic therapy is associated with the risk of developing therapy-related myeloid neoplasm (t-MN). From a German Hodgkin study group report, the median time and age from HL treatment to diagnosis of t-AML/MDS was 31 months and 43 years old, respectively. In our case, the patient had developed the t-AML after 48 months of treatment and age-onset is comparable to other reported cases. This study also stated that patients who received 4 or more cycles of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) had an increased risk of developing t-AML/MDS when compared with patients receiving less than 4 cycles of BEACOPP or no BEACOPP chemotherapy (6). For this patient, she obtained nearly all the drugs included in the BEACOPP regime.

The t(11;17) has been commonly reported in approximately 2% of variant Acute Promyelocytic Leukaemia cases, which also involved 11q23 but carry a *PLZF* fusion gene alternative to the *RARA* (7). In our case, the t(11;17)(q23;q25) was detected and found similar in a reported case of de novo Acute Monocytic Leukaemia and the FISH showed *MLL/SEP9* fusion transcripts in which, despite of intensive therapies, including haematopoietic stem cell transplantation, leukaemia progressed rapidly after a short complete remission. Thus, this translocation may be associated with poor prognosis (4)(8).

The 11q changes other than t(9;11) were associated with a significantly higher risk of treatment failure and death (9). However, bone marrow remission status evaluation cannot be ascertained as the patient died while on induction chemotherapy.

In most cases of classical therapy-related myeloid neoplasm, clonal chromosome abnormalities are also often associated with complex karyotyping. Surprisingly, over 90% of cases reported a loss of part or all of chromosomes 5 or 7 (10). While leukemias secondary to agents targeting DNA topoisomerase II (includes etoposide, doxorubicin, mitoxantrone) usually results in translocations involving the *MLL* gene on chromosome 11, band q23 (10)(11). This patient received 14 cycles of DNA topoisomerase II inhibitor which may be contributing to the translocation involving 11q23.

The management of t-AML depends on the stratification of the patient's age, performance status, co-morbidities and presence of clonal cytogenetic abnormalities similar to other subtypes of AML. The patients also should be considered for dose-reduced regime allogeneic stem cell transplantation, although it has been stratified as favourable prognosis (2),(12).

CONCLUSION

Patients who had received multiple chemotherapy regimens including Hodgkin lymphoma, shall be follow-up regularly to detect any early complication of therapy-related myeloid neoplasm, including AML and MDS, so that early intervention could be initiated. Besides, bone marrow morphological assessment is also essential in case of prolonged pancytopenia following treatment.

Conflict of interest

No conflict of interest was declared by the authors.

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