Case Report

Malignant Melanoma: A Double Malignancy or Second Malignant Neoplasm in a Patient of Acute Lymphoblastic Leukemia Following Therapy with a Composite Karyotype

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy of lymphoid origin seen with a peak incidence between 2 and 5 years. New drug regimen has increased the cure rate, although the risk of developing a second malignancy still persists. The common second malignant neoplasms in survivors of childhood ALL are hematolymphoid malignancies, central nervous system tumors, carcinomas, sarcomas, and bone tumors with a median latency of at least 10 years. There are also examples of nonmelanotic skin tumors such as basal cell carcinoma following ALL chemotherapy, but malignant melanoma is an extremely uncommon malignancy encountered. Melanoma is associated with genetic mutations such as CDKN2A, and CDK4 with an increased prevalence of second malignancy such as the lung, pancreas, and breast. However, double malignancy of melanoma with ALL is rare. Here, we report a rare case of malignant melanoma following ALL therapy associated with composite karyotype and early relapse.

Keywords: *Acute lymphoblastic leukemia, malignant melanoma, second malignancy*

Introduction

Hematolymphoid malignancies are the most common childhood cancers. Among which, acute lymphoblastic leukemia (ALL) affects both children and adults with a peak prevalence between 2 and 5 years. The most common type of ALL is pre-B-cell ALL.[1] Although cure rate of ≥80% is achieved with current intensive regimens, almost one-third of all deaths of childhood ALL are caused by toxicities of drugs or second malignant neoplasm (SMN).[2-6] The cumulative incidence of SMN varies from <1% to >10% in different studies, probably, due to the therapy regimen, duration, follow-up period, and prophylactic radiation,[3,7,8] whereas multiple primary cancer (MPC) is defined as more than one tumor diagnosed in the same patient, either simultaneously or sequentially. MPC should fill the diagnostic triad of: (1) the cancer must be clearly malignant as determined by histological evaluation; (2) each cancer must be geographically separated and distinct; (3) the possibility that the second tumor represents a metastasis should be excluded.[9] Herein, we report a rare case of SMN or MPC in a child diagnosed with ALL and developed malignant melanoma after 3½ months of the initial diagnosis following chemotherapy.

Case Report

A 10-year-old girl child presented to the department of hematology with petechial rashes all over the body for 10 days associated with fever, bilateral leg, and abdomen pain for 3–4 days. Routine hemogram revealed hemoglobin: 8.6 g%, total leukocyte count: 83.35 × 10^9/L, and total platelet count: 42 × 10^9/L. Peripheral smear [Figure 1a and b] showed the presence of blasts, which on differentials accounted for 80% and provisionally diagnosed to be a case of leukemia. Bone marrow aspiration revealed increased cellularity with the presence of blasts accounting for 86% of all nucleated cells, having high nuclear-cytoplasmic ratio (N: C ratio), scanty agranular cytoplasm, round-to-irregular nuclei, and inconspicuous nucleoli. Bone marrow biopsy shows dense interstitial infiltrate of the blast [Figure 1c and d]. Ultrasonography of the abdomen

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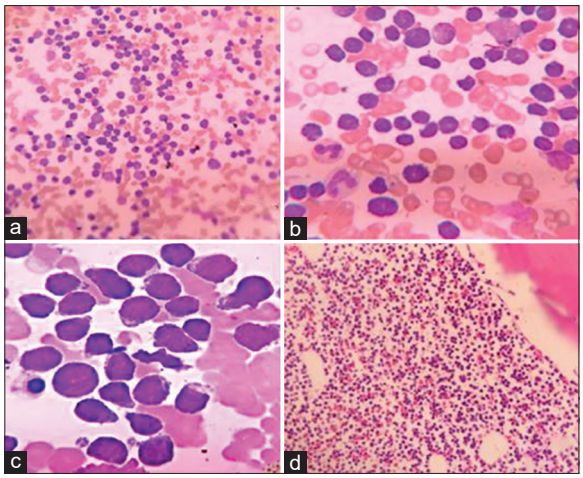

Figure 1: (a and b) Peripheral smear (×40, ×100 [oil]) and (c) Bone marrow aspiration (×100) reveals blasts with high N: C ratio, scanty agranular cytoplasm, round-to-irregular nuclei, and inconspicuous nucleoli (d) bone marrow biopsy shows dense interstitial infiltrate of the blast (×40)

revealed hepatosplenomegaly with multiple enlarged retroperitoneal nodes. She had no family history of malignancy.

Flow cytometry of bone marrow sample showed the gated population of 59.1% blasts and dim positivity for CD45 with low Side SCatter (SCC) and positive for CyCD79a, CD19, CD10, CD58 (dim positivity), CD33, and HLA-DR. Flow cytometry impression was precursor B-cell ALL. Fluorescent *in situ* hybridization analysis of bone marrow sample was negative for t (9;22) (i.e., BCR-ABL1 fusion gene), t (12;21) (i.e., TEL/AML1 fusion gene), and MLL gene rearrangement. Chromosomal analysis of heparinized bone marrow sample was performed by GTG banding technique (conventional karyotyping), which revealed a composite karyotype, i.e., 44-45, XX, t (1;7)(q21;p15), add (6)(q27),-14,-15,-18,-21[cp09]/45, XX, add (6)(p25), t (9;13)(p13;q14),-14[01]/46, XX[05]. Sixty percent of the cells showed reciprocal translocation between the long arm of one of the chromosome 1 and the short arm of one of chromosome 7, between the regions q21 and p15. Other chromosomal abnormalities found were, addition of material of unknown origin attached to one of the chromosomes 6 at the region q27 and loss of copy of varied chromosomes.[Figure 2]. Approximately 06% cells showed addition of material of unknown origin attached to the short arm of one of the chromosomes 6 at region p25 and reciprocal translocation between the short arm of chromosome 9 and the long arm of chromosome 13..

Chemotherapy was started according to the ICICLE protocol, and symptomatic management was done. Then, after day 35, the patient was followed up with bone marrow flow cytometry to access minimal residual disease (MRD). Her total leukocyte count was reduced to 9900/µl, B-ALL MRD was <0.01% and was declared cure of treatment, and she was put on maintenance therapy.

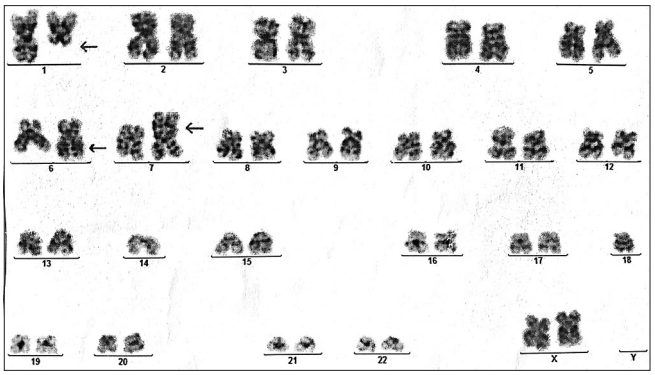

Figure 2: Karyotype showing reciprocal translocation between the long arm of one of the chromosome 1 and short arm of one of chromosome 7. Addition of material of unknown origin to one of chromosome 6 at region q27 (arrow)

After 3½ months of the initial diagnosis following chemotherapy, the child developed a nodular blackish lesion [Figure 3a] of 3 cm in maximum dimension, irregular margin, surface changes, and speckling in the left scapular region. With a clinical diagnosis of seborrheic keratosis, a punch biopsy was taken. Histopathology and immunohistochemistry confirmed the diagnosis of malignant melanoma [Figure 3b-d]. After that wide local excision was done with free margins and tumor bed.

Shortly after that, again, she presented with pain in the leg and hip joint. Bone marrow trephine biopsy was done with difficulty due to dry tap. The imprint cytology of which was markedly hypercellular with 87% blasts, and biopsy report revealed hypercellular marrow with interstitial infiltrate of immature cells of similar morphology. The final impression of relapsed acute leukemia was given, and unfortunately, the patient succumbed to death within 7 months of follow-up period.

Discussion

Depending on the time interval between two malignancies, MPC can be synchronous; when two or more tumors occurring within 6 months of each other or metachronous/heterochronous; if second cancer occurs >6 months after the first.[10] The risk of MPC is due to genetic and environmental factors, and some studies reported genes, including BRCA2, ATM, POLD1, PABL2, SMAD4, and so on, along with that microsatellite instability phenotype played an important role in the occurrence and pathogenesis of multiple primary malignant tumors (MPMTs).[11-13] The incidence of MPC has been reported to range from 0.52% to 11.7% in various studies from different countries.[14] Synchronous double malignancies involving the hematopoietic system and solid organ are even still rarer. Although these cases are usually reported as case reports, in a study by Cui *et al*., it accounted for 0.5% of all newly diagnosed cancer patients during their study period.[15]

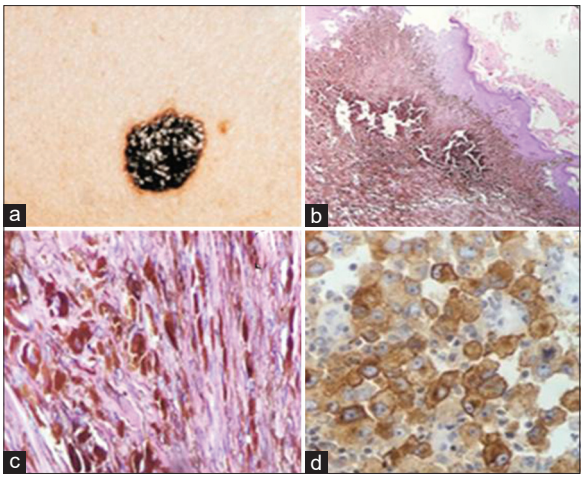

Figure 3: (a) Nodular blackish lesion of the back. (b and c) microscopy ([×10], [×40]): shows round-to-polygonal tumor cells infiltrating the lower epidermis and dermis, containing conspicuous eosinophilic nucleoli and abundant extra- and intracytoplasmic melanin deposit. (d) Immunohistochemistry-HMB 45 positivity (×40)

SMN is a rare complication of ALL therapy. Schmiegelow *et al*., in their large series of SMN in ALL patients, reported that hematolymphoid malignancy is the most common, followed by central nervous system (CNS) tumors, carcinomas, sarcomas, and bone tumors. They observed 11 cases (11/642) of melanoma with a median age interval of 10 years of diagnosis of ALL.[7] Hijiya *et al*. reported one case of malignant melanoma (0.6%) which occurred after the relapse of ALL, and they demonstrated that the cumulative incidence of the second neoplasm was 4.17% at 15 years and increased substantially after 20 years, reaching 10.85% at 30 years, representing a 13.5 fold increase in the overall risk with comparison to the general population.[3] Neglia *et al*., in their study, observed a median age of 6-year interval of SMN, and CNS neoplasm was the most common, followed by hematolymphoid malignancies. They found one case of melanoma in their miscellaneous category.[8]

Melanoma is a complex heterogeneous malignancy with risk factors such as environmental, genetic, and phenotypic. Melanoma-prone families having mutations in CDKN2A and CDK4 have an increased prevalence of a broad spectrum of cancers such as lung, pancreatic, and breast cancer, but its association with ALL is not described.[16] The common solid tumors are cancer esophagus, stomach, colon, and breast, and hematological malignancies reported were multiple myeloma (MM), myelodysplastic syndrome (MDS), Non Hodgkin Lymphoma (NHL), and chronic myeloid leukemia (CML).[15]

The presentation of malignant melanoma as the second synchronous malignancy in a young patient of ALL is extremely rare. After extensive searching of the English literature, to the best of our knowledge, this case is supposed to be the first case of these unusual associations. Therefore, a larger series with long-term follow-up is required to unfold the biological behavior.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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