Acute Monoblastic Leukemia as a Second Malignancy After Doxorubicin and Cisplatin Treatment for Osteosarcoma

Sinan Mahir KAYIRAN, Namık ÖZBEK

Department of Pediatrics, Başkent University Faculty of Medicine, Ankara, TURKEY

ABSTRACT

Secondary or therapy-related acute myeloid leukemia (t-AML) occurs as a complication of various chemotherapy regimens. In pediatric age group, leukemia as a second malignancy after osteosarcoma treatment with doxorubicin and cisplatin is relatively rare. A 15-year-old girl was admitted to our hospital with signs and symptoms of leukemia. She had been treated one-year earlier with doxorubicin and cisplatin for osteosarcoma of the left femur. The patient was diagnosed with acute monoblastic leukemia on the basis of bone marrow examination and immunophenotype analysis. There were no cytogenetic abnormalities. The patient’s father had been diagnosed with pelvic chondrosarcoma, which suggested a familial susceptibility to cancer. We interpreted this as a rare case of t-AML with normal cytogenetic analysis, and believe the disease was induced by the addition of platinum compounds to a regimen including topoisomerase II inhibitors.

Key Words: Therapy-related leukemia, Cisplatin, Doxorubicin, Osteosarcoma.

ÖZET

Doksorubisin ve Sisplatinle Osteosarkom Tedavisi Ardından İkincil Malignite Olarak Gelen Akut Monoblastik Lösemi


Anahtar Kelimeler: Tedaviye bağlı lösemi, Sisplatin, Doksorubisin, Osteosarcoma.


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INTRODUCTION

Leukemia occurring as a second malignancy after treatment of childhood malignancy is well recognized\[1\]. In most instances, the disease is of myeloid lineage and develops after chemotherapy and radiation therapy. The secondary leukemia known as therapy-related acute myeloid leukemia (t-AML) occurs as a complication of various chemotherapy regimens. This most often arises after leukemia and lymphoproliferative diseases and accounts for 10-20% of all AML cases\[2\]. The doxorubicin-cisplatin combination is a chemotherapeutic regimen that is commonly used in cases of osteosarcoma. Development of secondary leukemias after treatment of ovarian cancer with these two agents has been extensively reported and reviewed\[3,4\]. However, in pediatric age group, leukemia as a second malignancy in patients with primary osteosarcoma is relatively rare, and only isolated cases have been reported\[5,6\]. We report a case of secondary acute monoblastic leukemia that followed doxorubicin and cisplatin treatment for osteosarcoma.

A CASE REPORT

A 15-year-old girl was referred to pediatric hematology unit of our hospital with fever, abdominal pain, pallor, and gingival hypertrophy. Fourteen months earlier, she had had her left femur amputated due to osteosarcoma. She had received one presurgical cycle of chemotherapy with doxorubicin and cisplatin (100 mg/m² and 30 mg/m², respectively) and three cycles with the same agents and doses after amputation. The patient had remained well and in remission for one-year after the completion of chemotherapy, but then developed complaints of malaise, abdominal pain, and gingival hyperplasty. She was admitted to hospital with these signs of acute leukemia. The family history revealed that the girl’s father had undergone surgery for pelvic chondrosarcoma four-years earlier. Physical examination of the patient revealed aphthous stomatitis, gingival hyperplasty, abdominal tenderness and splenomegaly. The peripheral blood findings were as follows: Hemoglobin: 7.1 g/dL; white blood cell count: 232 x 10⁹/L, with 98% of monoblasts in the differential count; platelet count 6 x 10⁹/L. A bone marrow examination revealed hypercellularity with > 95% monoblasts. Immunophenotype analysis revealed: CD 13, 38.4%; CD 11B, 82.7%; CD 33, 98.6%; CD 45, 96.3%; CD 14, 50.7%. Based on these findings, she was diagnosed with acute monoblastic leukemia (AML-M5). Cytogenetic analysis revealed a 46 XX genotype with no chromosomal abnormalities. Other laboratory testing revealed elevated levels of blood urea nitrogen (56 mg/dL); creatinine (2.57 mg/dL), uric acid (25.1 mg/dL). The initial treatment was forced alkali diuresis and oral allopurinol. When the patient’s uric acid values normalized and the WBC count dropped below 40 x 10⁹/L, she was started on a remission induction protocol with prednisolone, cytosine arabinoside (ara-C) and daunorubicin. However, after 3 days of treatment the patient developed severe neutropenia and sepsis. She died 10 days later.

DISCUSSION

Many reports have identified acute leukemia as the most frequent therapy-related malignancy. The incidence of t-AML has increased in recent years due to long survival and intensive chemotherapy and irradiation protocols. Secondary leukemias have generally been divided into two groups: Those following treatment with alkylating agents, and those following topoisomerase inhibitor therapy. Alkylating agents are the main agents associated with the increased incidence of secondary leukemia. Cases that develop after exposure to these agents typically have a long latency period (5 or more years), are often preceded by a myelodysplastic syndrome (MDS) phase, and frequently show deletions or loss of chromosomes 5 and 7 on cytogenetic analysis\[7\]. In contrast, leukemias that follow exposure to topoisomerase II inhibitors usually have a short latency period (6-months-5-years), are not associated
with a prior MDS phase, and have monocytic or myelomonocytic morphology\(^8,9\). In our patient, the treatment-leukemia interval was relatively short in accord with topoisomerase II inhibitor induced secondary leukemia. The chemotherapy protocol that had been used was a doxorubicin-cisplatin combination. The most important mechanism of doxorubicin cytotoxicity is inhibition of topoisomerase II which results in breakage of DNA strands\(^10\). Cisplatin is a heavy metal complex that induces tumor cell death by cross-linking DNA strands in a manner analogous to that induced by alkylating agents. Reactive aquated intermediates form directly within cells and those intermediates covalently bind to DNA leading to DNA cross-links\(^11\). It is assumed that the addition of alkylating agents and platinum compounds to regimens containing topoisomerase II inhibitors may produce cumulative DNA damage sufficient to induce secondary leukemia\(^12\).

The occurrence of a second malignant neoplasm in patients treated for osteosarcoma has become an area of increasing concerns\(^13\)\-\(^18\). Bacci et al reported five patients who had a second neoplasm that was diagnosed 1 to 12 years (median, 6.1 years) from the beginning of treatment\(^19\). Two of these tumors were a lymphoblastic acute leukemia that became manifest 12 and 16 months from the start of treatment. They were treated for the leukemia and were alive and free of disease 8 and 10 years after the last treatment. The treatment-leukemia interval and the chemotherapy regimen and dosage were almost the same in our patient, but the leukemia was the monoclastic type. In 1988, Orazi et al reported a child who developed acute monoblastic leukemia 2 years after chemotherapy for osteogenic sarcoma\(^6\). In this case, cytogenetic study showed a hyperdiploid complex pattern in all metaphases with 48XY, dup 1 (q12), +3, +9. DeMuyck et al reported a similar case of t-AML with t(8;16) (p11;p13) following anthracycline-based therapy for nonmetastatic osteosarcoma\(^20\). The literature also documents cases of t-AML with no cytogenetic abnormality\(^21\),\(^22\). Similarly, the cytogenetic analysis in our case revealed no abnormalities. However, the fact that the patient’s father had pelvic chondrosarcoma suggested a familial cancer susceptibility, which points to the need for further genetic evaluation.

In conclusion, if patients treated for primary malignancies were followed up more closely, more patients with therapy-related leukemia would be detected. As this patient with normal cytogenetic analysis is one of the rare cases of AML in the literature suspected to be related to doxorubicin and cisplatin treatment for osteogenic sarcoma, clinicians must be wary of leukemogenic potential of these agents. This case and careful follow-up of others that follow similar courses might help confirm the hypothesis of cisplatin-related or doxorubicin-related secondary leukemias.

**REFERENCES**


Address for Correspondence:
Sinan Mahir KAYIRAN, MD
Başkent University Faculty of Medicine
Department of Pediatrics
6. Cadde, No: 72/3, 06490, Bahçelievler, Ankara, TURKEY
e-mail: sinannahir@yahoo.com