CASE REPORT

Concurrent Presentation of Therapy Related Acute Myeloid Leukemia in a Case of Neuroblastoma

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Received: 30 July 2014 / Accepted: 18 February 2015 / Published online: 25 February 2015
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Abstract Therapy related Acute Myeloid Leukemia/Myelodysplastic syndrome (t-AML/MDS) occur due to the direct mutational events of the chemotherapeutic agents and radiotherapy. The disease latency, mutational events and prognosis vary with the type of chemotherapeutic agent. Therapy related Acute Myeloid Leukemia occurring with DNA topoisomerase II inhibitors have a shorter latency period and poor prognosis than anthracyclin based regimens. We report a case of a 9 year old boy who developed t-AML with mixed-lineage-leukemia gene translocation within a year of high dose chemotherapy for stage 4 neuroblastoma. He had residual mass of neuroblastoma in the abdomen and bone marrow. The patient expired within 2 weeks of induction chemotherapy.

Keywords Therapy related acute myeloid leukemia · Neuroblastoma

Introduction

Therapy related Acute Myeloid Leukemia and Myelodysplastic syndrome (t-AML/MDS) are a group of secondary malignancies developing in patients treated previously with chemoradiation for haematological malignancies or solid

tumours. With the increase in use of high dose chemotherapeutic regimens, higher cure rates and longer survival rate of patients with malignancies the incidence of secondary malignancies is increasing. The latency period of development depends on the group of drugs and dosage regimens. Therapy related Acute Myeloid Leukemia (t-AML) occurs due to mutations in the myeloid cell lineage caused by the cytotoxic drugs. Many of the mutations are common with de novo AML but unfavourable cytogenetics is more common in t-AML conferring a poor prognosis. We report a case of a 9 year boy with t-AML following treatment of neuroblastoma with both diseases in activity and unfavourable cytogenetics.

Case Report

Nine year old boy presented with right posterior cervical lymphadenopathy. Systemic examination was normal. Histopathological examination showed a partially effaced lymph node with few residual lymphoid follicles. The lymph node was infiltrated by a monotonous population of small blue round cells in a eosinophilic fibrillary background (Fig. 1). These cells were positive for neuron specific enolase, chromogranin and synaptophysin, negative for CD 99, Tdt, leukocyte common antigen and desmin. The features were diagnostic of metastatic neuroblastoma. On further imaging the primary was found in the left suprarenal region with multiple retroperitoneal nodes and skeletal metastasis. Bone marrow biopsy showed metastatic neuroblastoma with grade 2 fibrosis. The patient was started on CCG 3891 protocol (Adriamycin, Etoposide, Cyclophosphamide, Cisplatin) for stage 4 neuroblastoma under the high risk category. MIBG scan after 8 months of treatment showed residual lesion in the

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Fig. 1 Section shows lymph node partly effaced by small blue round cells in a fibrillary background. Arrow points to the residual germinal centre (H & E $\times 100$). Inset shows high power view of the small blue round cells with nuclear smudging. (H & E $\times 400$). (Color figure online)

abdomen. Trucut biopsy of the lesion showed residual neuroblastoma with ganglionic and schwannian differentiation. He was advised palliative therapy with *cis*-retinoic acid but defaulted. After 2 months patient returned with left arm abscess and multiple vesicles diagnosed as herpes simplex infection in the dermatology department. He had pallor and mild hepatosplenomegaly. Routine complete hemogram showed haemoglobin—8 g/dl, WBC count— $10 \times 10^9/L$ with 47 % myeloblasts positive for Sudan Black B and platelet count— $51 \times 10^9/L$. Bone marrow aspiration had 80 % myeloblasts without maturation and 6 % plasma cells (Fig. 2). Bone marrow biopsy was hypercellular replaced by blasts (Fig. 3) which were positive for CD 34, MPO, CD 117 (Fig. 4a, b) and negative for Tdt. In addition there was a small focus (5 %) of small round cells in a fibrillary background (Fig. 3) positive for neuron

Fig. 2 Bone marrow aspirate smear showing myeloblasts (Leishmann $\times 400$)

Fig. 3 Bone marrow biopsy showing near total replacement by blast with a small acellular fibrillary focus (arrow) (H & E $\times 400$)

specific enolase (Fig. 5a), chromogranin (Fig. 5b) and synaptophysin. This focus was negative for the myeloid markers. The diagnosis of acute myeloid leukemia without maturation (FAB-AML M1) with residual focus of metastatic neuroblastoma was made. The blasts were positive for CD 117, CD 13, CD 33, CD 34 and HLA DR in flow cytometry. Cytogenetics showed 46XY t(11;19) (q23;q23), t(21;21) (q10;q10) (Fig. 6a). Residual left suprarenal mass, multiple skeletal lesions were found in MIBG I 131 scan (Fig. 6b). With the final diagnosis of t-AML with MLL gene translocation and residual neuroblastoma the patient was started on daunorubicin and cytarabine. On the second week of therapy he developed profound neutropenia, pneumonia and succumbed to illness.

Discussion

Neuroblastoma is an embryonal tumour arising from the neural crest cells. It accounts for 6 % of childhood malignancies [1].

Treatment includes surgery, radiotherapy, conventional chemotherapy and recently high dose chemotherapy. With increasing success in therapy with high dose regimens the incidence of complications and secondary malignancies are high. Secondary malignancies in treated cases of neuroblastoma described in literature includes thyroid tumor, osteogenic sarcoma, soft tissue sarcoma, acute myeloid, lymphoid leukemias and brain tumour [2].

Therapy related acute myeloid leukemia occurs due to the direct mutational effects of the chemotherapeutic agents. It is divided into two subgroups. The one following

Fig. 4 a, b Myeloblasts positive for CD 117 and MPO. The focus of neuroblastoma metastasis is negative (IHC $\times 400$)

Fig. 5 a, b Metastatic focus of neuroblastoma positive for neuron specific enolase and chromogranin (IHC $\times 400$)

treatment with alkylating agents have a latency period of 5–10 years, preceded by a phase of myelodysplasia and associated with monosomy 5 or 7. t-AML occurs earlier with DNA topoisomerase II inhibitors within 1–2 years and have balanced chromosomal translocations most commonly involving the MLL (mixed-lineage-leukemia) gene at chromosome band 11q23 or less commonly AML1 gene on 21q22 [3]. Our patient had the second type of presentation with balanced translocations of 11q23 and 12.

The mixed-lineage-leukemia (MLL-11q23) gene is a promoter of gene expression in early embryonic development and hematopoiesis. Balanced translocations of 11q23 are seen in primary and majority of secondary acute myeloid leukemia following treatment with DNA topoisomerase II inhibitors. The fusion partner genes vary. Seventy chromosome partners of 11q23 have been identified [10-11q23]. The resulting chimeric protein leads to gain of function and leukemogenesis. The partner gene t (11;19) seen in our patient constitutes 5 % of the 11q23 rearrangements. Childhood AML with this translocation has an intermediate prognosis [4].

There are only two case reports of simultaneously active neuroblastoma and secondary acute leukemia in literature. Telma et al. reported a 4 year old boy with stage 4 neuroblastoma in partial remission with acute myelomonocytic leukemia [5]. Pedram et al. reported a case of both neuroblastoma with secondary acute lymphoblastic leukemia in activity [6]. But these cases had residual lesion at the primary site. The most interesting finding in our case is the presence of a focus of neuroblastoma amidst the leukemic cells in the bone marrow biopsy.

Fig. 6 **a** Cytogenetics showing 46XY t(11;19)(q23;q23), t(21;21)(q10;q10). **b** shows residual neuroblastoma lesions in MIBG scan

To the best of our knowledge, simultaneous presence of a focus of neuroblastoma and myeloid leukemia in the same site of bone marrow biopsy, has not been reported previously. This finding was serendipitous, was made while screening the CD 117 stained trephine biopsy slide. Few hypocellular areas were noticed which were negative for CD 117 staining, as well as for CD 34 and MPO. A closer look at the hematoxylin and eosin stained section, followed by Synaptophysin and the other neural markers confirmed these foci to be residual neuroblastoma cells.

The prognosis of therapy related AML is poor. Hence chemotherapeutic regimens with less therapy related complications are in need especially with the increase in the long term survival of cancer patients.

Conflict of Interest None.

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