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LETTER TO THE EDITOR

Concurrence of relapsed neuroblastoma and therapy-related acute myeloid leukemia in an 8-year-old patient

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Dear Editors,

Therapy-related myeloid neoplasms, including therapy-related cases of acute myeloid leukemia/myelodysplastic syndrome (t-AML/MDS) and myelodysplastic/myeloproliferative neoplasm(t-MDS/MPN), occur as a late complication of chemotherapeutic agents and/or radiotherapy due to a prior neoplastic or non-neoplastic diseases. Recently reported data indicate that nearly 70% have been treated for a solid tumor [1]. Neuroblastoma is the most frequent extracranial solid tumor in early childhood, particularly in the first year of life. The simultaneous discovery in the same patient of neuroblastoma and leukemia is very rare. Herein, we report a concurrence of relapsed stage 4 neuroblastoma and t-AML in an 8-year-old boy, within a year of high-dose chemotherapy for the neuroblastoma.

An 8-year-old boy was admitted to our hospital with a 16-month history of stage IV neuroblastoma (poorly differentiated), and presenting as relapsed neuroblastoma with bone marrow involvement for more than 3 months. At the initial presentation, the right adrenal resection was performed and postoperative pathology revealed the abnormal cells with a positivity of neuron-specific enolase, chromogranin, and synaptophysin. After the initial confirmed diagnosis of neuroblastoma, the boy began chemotherapy with CAV (cyclophosphamide + doxorubicin + vincristine), CVP (cisplatin + etoposide), and regimens of cyclophosphamide + Topotecan. However, he soon relapsed presenting bone marrow involvement after the initial treatment of chemotherapy for 1 year. At the relapsed period, the child presented with repeated fever and leg pain, accompanied by gingival hyperplasia and purplish red skin papules. He had a mild anemia with a hemoglobin concentration of 83 g/L, thrombocytopenia of 31×10^9/L, and a marked leukocytosis of 64×10^9/L. Blasts in blood smear (accounting for 86%) showed a high nucleocytoplasmic ratio with plenty of cytoplasms, containing oval nuclei with finely reticulated nuclear chromatin (Fig. 1a). At low magnification, bone marrow (BM) smear was cellular. Normal cells were replaced by leukemic cells (7.5% monoblasts and 89.5% promonocytes) and clumps of unclassified cells, and nuclear molding was evident in some parts of the film (Fig. 1b). Higher magnification showing the morphological features of blasts were identical to those shown in peripheral blood smears (Fig. 1c). In addition, morphological details of infiltrates demonstrated abnormal cells exhibiting molding of nuclei by adjacent cells varying from 10 to 20 cells without fibrillar extracellular material (Fig. 1d). The overall morphology was suggestive of coexistence of a non-hemopoietic neoplasm with acute myeloid leukemia. Immunophenotyping by flow cytometry demonstrated two distinct populations of abnormal cells. A large population of CD45dim cells shown in red comprising over 90% of total nucleated cells were CD64 +, CD33 +, CD81 +, CD9 +, CD15 +, CD13 +, CD4 +, HLA-DR partial +, CD11b partial +, and CD14 −. They were identified as promonocytes. The minority population of CD45 − cells shown in blue (accounting for 0.69%) were CD81 +, CD56 +, GD2, CD15, and CD9 partial +, suggesting a non-hemopoietic neoplasm (Fig. 2). MYCN amplification was detected by fluorescent in situ hybridization (FISH), and gene mutation screening showed a positivity of NRAS Q61R mutation. G banding analysis showed a complex karyotype:46, XY, add (17) (p13) [7] /46, idem, add (1) (p36.1) [2] /46, idem, i (7) (q10) [3] /46, idem, del (11) (q23) [4] /46, idem, t (2;4) (q11.2; p16), del (14) (q24) [1] /46, Idem, del (9) (q13q22) [1] /46, Idem, add (12) (p13) [1] /46, Idem, t (11; 12) (q13; q24.1) [1] /46, Idem, t (9; 12) (p13; q13) [1]. Taken together, the diagnosis of simultaneous neuroblastoma

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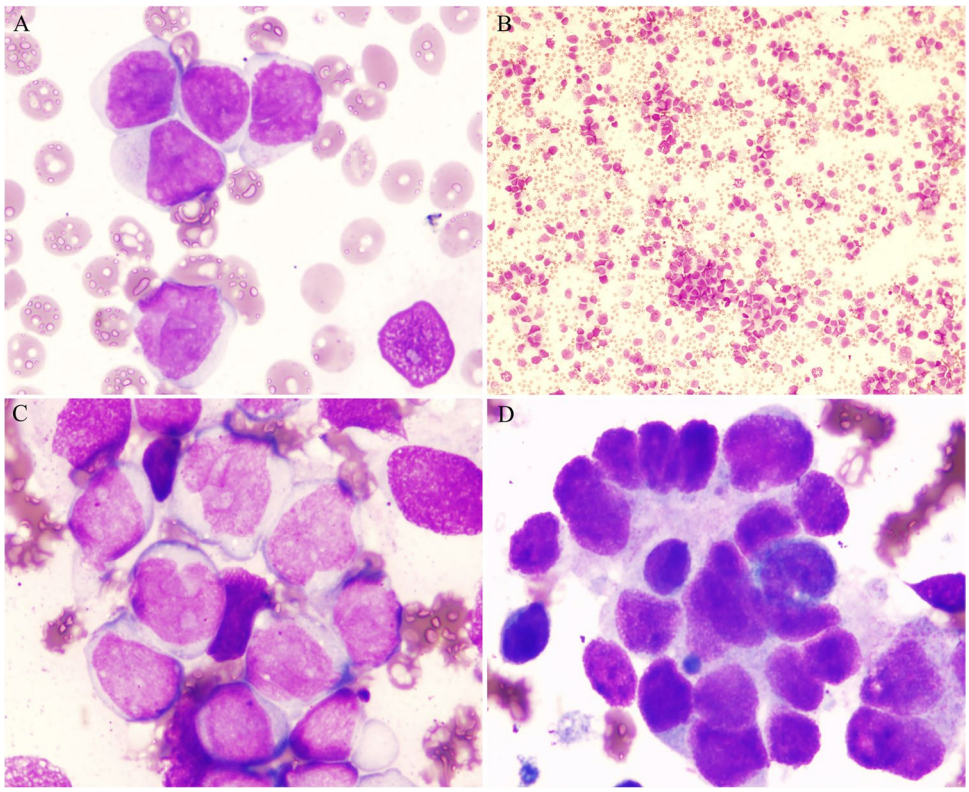

Fig. 1 Peripheral blood smear revealed blasts (accounting for 86%) showing a high nucleocytoplasmic ratio with plenty of cytoplasms, containing oval nuclei with finely reticulated nuclear chromatin **a** Wright-Giemsa × 1000. At low magnification, the BM smear was cellular. Normal cells were replaced by leukemic cells (7.5% monoblasts and 89.5% promonocytes) and clumps of several cells displaying nuclear molding were evident in some parts of the film **b** Wright-Giemsa × 400. Higher magnification showing the morphological features of blasts were identical to those shown in peripheral blood smears **c** Wright-Giemsa × 1000, morphological details of infiltrates demonstrated abnormal cells of neuroblastoma exhibiting molding of nuclei by adjacent cells varying from 10 to 20 cells without fibrillar extracellular material **d** Wright-Giemsa × 1000

and AML was made. Of interest, both the morphology and immunophenotype of the initial presentation were similar to the relapsed presentation.

Neuroblastoma is an embryonal solid tumor of neuroectodermal cells originated from the neural crest and distributed in the adrenal medulla and sympathetic nervous system, accounting for approximately 6% of childhood malignancies [4]. The fundamental biology of the three most frequently abnormalities included 1p loss, 17q gain, and N-MYC amplification [3]. Although the child underwent timely treatment of surgery and chemotherapy, he relapsed within a year. High-dose chemotherapy is a double-edged sword, it can improve the cure rate and prolong the survival time of patients, but at the same time, it also increases the incidence of secondary tumors. T-AML/MDS are a group of secondary malignancies developing in patients previously treated with chemoradiation for hematological disorders or solid tumors. To date, two subsets of t-AML/MDS are generally recognized clinically, one group occurs 5–10 years after exposure to alkylating agents and/or radiation, preceded by a phase of myelodysplasia and associated with unbalanced translocation, most commonly monosomy 5 and/or 7, as well as complex karyotypes and mutations or loss of TP53. The second subset has a shorter latent period with 1–5 years, following treatments with DNA topoisomerase II inhibitors therapy. This group accounting for 20–30% of patients, frequently harbors balanced chromosomal translocation, involving rearrangements of 11q23, but without the presence of the preceding MDS phase [2]. Our patient was regarded as the second type, due to the presence of complex karyotypes, and a medication history of etoposide and doxorubicin.

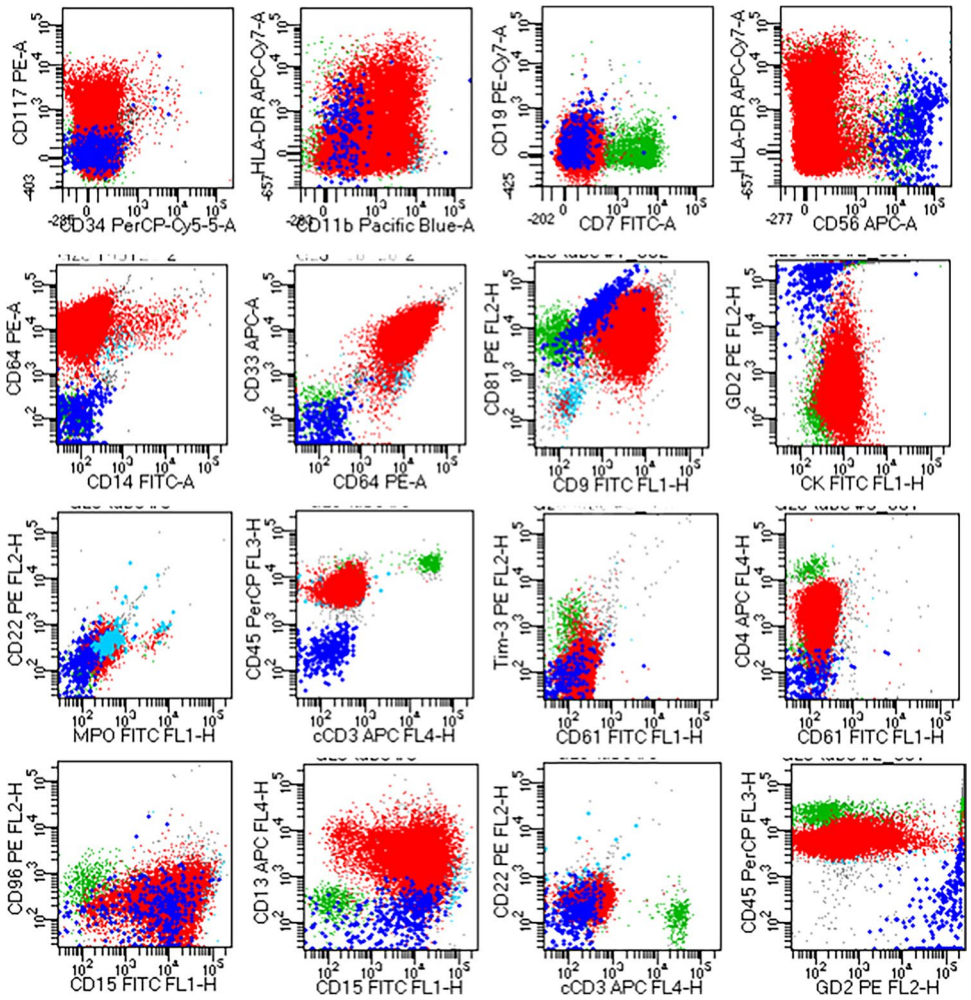

Fig. 2 A CD45 versus SSC analysis revealed a large population of CD45dim cells shown in red comprising over 90% of total nucleated cells and were CD64 +, CD33 +, CD81 +, CD9 +, CD15 +, CD13 +, CD4 +, HLA-DR partial +, and CD11b partial +. They were therefore identified as being of monoblastic lineage. The minority population of CD45 − cells shown in blue (accounting for 0.69%) was CD81 +, CD56 +, GD2, and CD9 partial +, suggesting a non-hemopoietic neoplasm

The most interesting observation in this case is the presence of clusters of neuroblastoma cells amidst the leukemic cells in the bone marrow aspiration smears, with the presence of MYCN amplification and an absence of 1p deletion. Amplification of MYCN is well known to correlate with advanced-stage disease and established as a powerful clinical biomarker of high-risk disease. And it was firmly implicated in the malignant aggressiveness of neuroblastoma tumors. To date, very few cases of concomitantly neuroblastoma and t-AML have been reported [5, 6]. In summary, this is a very unusual pediatric case of concurrence of relapsed neuroblastoma and therapy-related acute myeloid leukemia.

Author contribution All authors contributed to the paper conception and design. Clinical and histological data were collected by Ping Wu, Man Chen, and Minjing Fu. Histological diagnosis and study design were performed by Aixian Wang and Hui Wang. The draft of the manuscript was written by Ting Li and Hui Wang, and all authors read and approved the final manuscript.

Declarations

Ethics approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from this patient.

Consent for publication Informed consent was obtained for the publication.

Conflict of interest The authors declare no competing interests.

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