

Second malignant neoplasm in a treated Ewing sarcoma patient: A case report

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Received - 07 May 2018

Initial Review - 05 June 2018

Accepted - 26 June 2018

ABSTRACT

Ewing sarcoma (ES) is an aggressive tumor commonly seen in children and young adults. Late effects of ES therapy include the second cancers, a tragic outcome for survivors of such young age. We report a case of a 3-year-old male child who presented with a right maxillary mass extending to the orbit. Fine-needle aspiration cytology and tru-cut biopsy showed features suggestive of a small round cell tumor. Immunohistochemistry confirmed the diagnosis of ES/primitive neuroectodermal tumor. The patient was started on non-metastatic Ewing family tumor protocol with intensity-modulated radiotherapy and responded well to therapy. He was followed up regularly, but after 5 months of initial diagnosis, his peripheral blood smear showed atypical cells resembling blasts. His bone marrow aspiration (BMA) and biopsy showed marrow infiltrated by hematolymphoid malignancy. Based on the positivity of the blasts for myeloperoxidase and non-specific enolase in cytochemistry on the BMA and flow cytometric analysis, a diagnosis of acute myeloid leukemia with monocytoid differentiation was made. We report this case to emphasize the role of the pathologist in differentiating the second malignancies from recurrence of the first malignancy or therapy-related changes, especially in the case of an equivocal morphological picture.

Key words: *Chemotherapy, Ewing, Malignant, Radiotherapy, Sarcoma, Second*

Ewing sarcoma (ES) is a rare aggressive tumor commonly seen in children and young adults that have a tendency toward early dissemination to the lungs, bone, and bone marrow and are responsive to chemotherapy and radiation therapy (RT). Late effects of ES therapy include the second cancers, a tragic outcome for survivors of such young age.

CASE REPORT

A 3-year-old child presented to the department of medical oncology with a right maxillary mass extending to the orbit. Hematological parameters were within normal range. A fine-needle aspiration cytology was done which revealed a small round cell tumor. This was followed by a tru-cut biopsy of the mass which showed sheets of small round tumor cells with fine chromatin, inconspicuous nucleoli, and scant to moderate cytoplasm, many showing clearing. Occasional interspersed vessels with peritheliomatous pattern were also observed. The panel of round cell tumor immunohistochemistry (IHC) markers was run and revealed the membranous of CD99 and nuclear positivity of FLI-1 antigen along with focal positivity of cytokeratin, while CD45, desmin, myeloperoxidase (MPO), myogenin, synaptophysin, and chromogranin were negative. Based on the morphology and typical IHC markers positivity, the final diagnosis of ES/primitive neuroectodermal tumor was offered.

After the complete metastatic workup, the patient was treated on non-metastatic Ewing family tumor chemotherapy protocol

with intensity-modulated radiotherapy. The patient responded well after the initial treatment and was followed up regularly. When he came for his subsequent visits after 5 months, his complete blood counts revealed a high total leukocyte count, and the peripheral smear showed atypical cells resembling blasts up to 58%. His bone marrow aspirate smear showed blast around 52%, the morphology of which did not permit a categorization of myeloid or lymphoid lineage.

The bone marrow aspiration and biopsy were reported as marrow infiltrated by hematolymphoid neoplasm. Flow cytometry findings and positivity for neuron enolase and MPO stain in blasts were consistent with acute myeloid leukemia (AML) with monocytoid differentiation with a small subset of blasts expressing cytoplasmic CD79a, CD22, and CD19. No other lymphoid markers showed positivity. Cytogenetic studies did not reveal any gross genetic abnormality except for a 6 bp insertion in the TAD2 domain of CEBPA. This probably represents a polymorphism.

Treatment for AML was instituted at our center, but after an initial response, his condition deteriorated and 3 months into therapy, he succumbed to secondary infections.

DISCUSSION

The second malignant neoplasms (SMNs) are generally defined as cancers which develop in patients with more than two distinct histologic types occurring at least 6 months after the

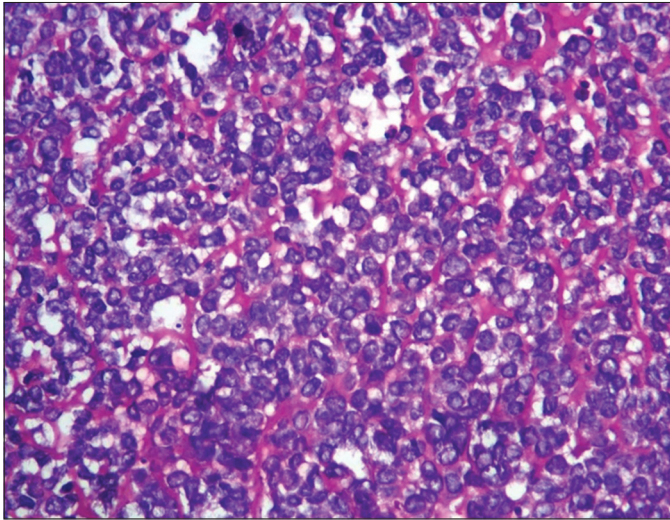


Figure 1: Round cell tumour. H&E, x200

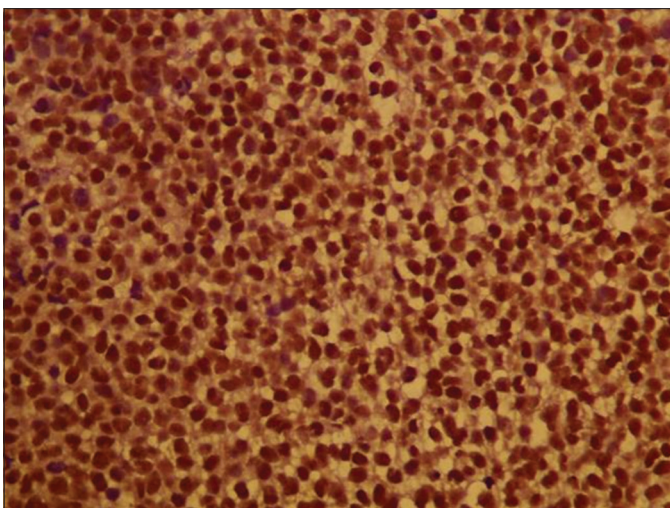


Figure 2: Nuclear positivity of FLI-1. IHC, x200

diagnosis of the initial malignancy [1]. Previous therapy, genetic susceptibility, and the type of the first cancer are known to be associated with the risk of an SMN among patients treated for a childhood cancer [2]. Independent of initial treatment and any familial cancer syndrome, a significantly increased risk of developing any SMN was observed after Hodgkin's lymphoma, retinoblastoma, soft tissue sarcoma, and a malignant bone tumor as the first malignant neoplasm [2].

Treatment-related SMN in ES patients varies from soft tissue sarcomas in radiotherapy treated patients to hematological malignancies in patients treated with intensified chemotherapy regimens containing high-dose alkylators and epipodophyllotoxins, which are known to cause secondary leukemias [3]. Among the solid tumors, a report of British survivors suggests that the risk of bone tumor, especially osteosarcoma as SMN was higher after ES treatment than other childhood cancers followed by many other tumors such as retinoblastoma, neuroblastoma, neuroepithelioma, teratocarcinoma, germinoma, endometrial sarcoma, liposarcoma, spindle cell sarcoma, dermatofibrosarcoma, fibrosarcoma, undifferentiated sarcoma, malignant melanoma,

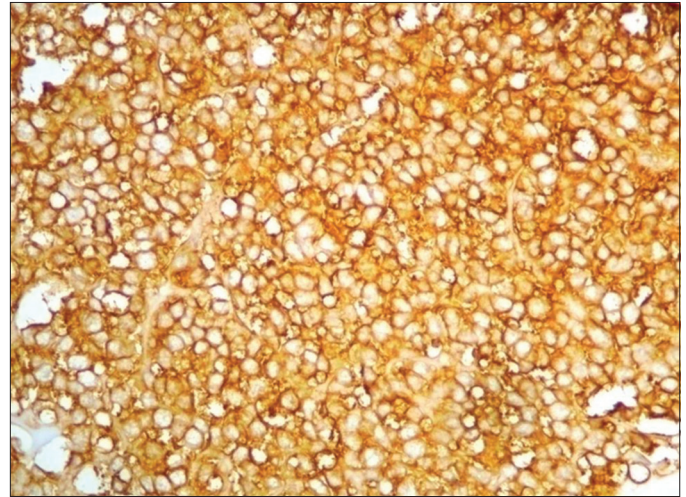


Figure 3: Membrane positivity of CD99. IHC, x200

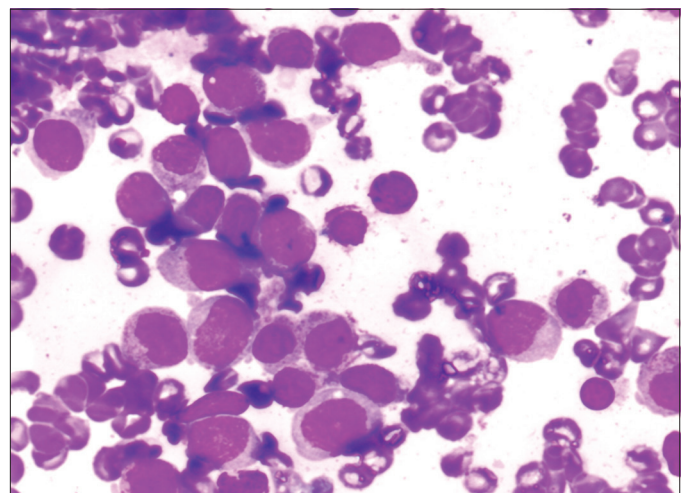


Figure 4: BMA showing atypical blasts like cells (Leishman stain, x200)

anaplastic astrocytoma, breast cancer, clear cell adenocarcinoma, papillary thyroid cancer, renal cell carcinoma, malignant thymoma, palatal and parotid mucoepidermoid carcinoma, colon cancer, gastric adenocarcinoma, bronchioalveolar carcinoma, and small cell lung cancers [4-9].

Several of these solid tumors, SMNs occurred far from the radiation field or in patients who received no RT. They may have factors known to predispose to the development of multiple malignancies such as the familial form of retinoblastoma and neurofibromatosis. The most common hematologic SMN in literature was found to be AML/MDS, which comprises about 60% of the cases while others being B-cell and T-cell lineage ALL, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma [9,10]. Literature review also mentioned that hematologic SMNs generally have a shorter latency period than solid tumor SMN [3] as seen in our case where the interval was <6 months.

The attributable cause for leukemogenesis was intensified chemotherapy which causes DNA damage to hematopoietic stem cells forming atypical blasts perpetuated by G-CSF supplemented along with the chemotherapy regime. There are also higher than

expected rates of SMN not clearly related to treatment, suggesting that there must be mild to modest genetic contribution to the risk. Although ES is not a part of any clearcut cancer predisposition syndrome; these family of tumours have been shown to contain alterations in RB and p53 which are known to be mutated in hereditary RB and Li Fraumeni syndrome, respectively [11].

The role of pathologists is of utmost importance to differentiate the second malignancy from recurrence of the first malignancy or therapy-related changes, especially so in case of an equivocal morphological picture. ES survivors should be educated on the risk of SMN and followed up closely throughout their lifetime.

CONCLUSION

ES survivors are at significant risk for SMN, particularly sarcomas and other solid tumors in RT fields and for myeloid SMN after epipodophyllotoxin and alkylator therapy. In addition, the risk in these patients may be higher than in those treated for other childhood cancers, and it is likely related, in part, to ES therapy.

REFERENCES

1. Hunger SP, Sklar J, Link MP. Acute lymphoblastic leukemia occurring as a second malignant neoplasm in childhood: Report of three cases and review of the literature. *J Clin Oncol* 1992;10:156-63.
2. Guérin S, Hawkins M, Shamsaldin A, Guibout C, Diallo I, Oberlin O, *et al.* Treatment-adjusted predisposition to second malignant neoplasms after a solid cancer in childhood: A case-control study. *J Clin Oncol* 2007;25:2833-9.

3. Schiffman JD, Wright J. Ewing's sarcoma and second MALIGNANCIES. *Sarcoma* 2011;1:1-8.
4. Hawkins MM, Wilson LM, Burton HS, Potok MH, Winter DL, *et al.* Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst* 2012;88:270-8.
5. Goldsby R, Burke C, Nagarajan R, Zhou T, Chen Z, Marina N, *et al.* Second solid malignancies among children, adolescents, and young adults diagnosed with malignant bone tumors after 1976: Follow-up of a children's oncology group cohort. *Cancer* 2008;113:2597-604.
6. Paulussen M, Ahrens S, Lehnert M, Taeger D, Hense HW, Wagner A, *et al.* Second malignancies after ewing tumor treatment in 690 patients from a cooperative german/Austrian/Dutch study. *Ann Oncol* 2001;12:1619-30.
7. Navid F, Billups C, Liu T, Krasin MJ, Rodriguez-Galindo C. Second cancers in patients with the Ewing sarcoma family of tumours. *Eur J Cancer* 2008;44:983-91.
8. Li X, Li W, Mo W, Yang Z. Acute lymphoblastic leukemia arising after treatment of ewing sarcoma was misdiagnosed as bone marrow metastasis of ewing sarcoma: A case report. *Medicine (Baltimore)* 2018;97:e9644.
9. Van den Berg H, Heinen RC, Van der Pal HJ, Merks JH. Extra-osseous ewing sarcoma. *Pediatr Hematol Oncol* 2009;26:175-5.
10. Bhatia S, Krailo MD, Chen Z, Burden L, Askin FB, Dickman PS, *et al.* Therapy-related myelodysplasia and acute myeloid leukemia after ewing sarcoma and primitive neuroectodermal tumor of bone: A report from the children's oncology group. *Blood* 2007;109:46-51.
11. Hamelin R, Zucman J, Melot T, Delattre O, Thomas G. P53 mutations in human tumors with chimeric EWS/FLI-1 genes. *Int J Cancer* 1994;57:336-40.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Mudra KL, Zachariya C, Jagannath S. Second malignant neoplasm in a treated Ewing sarcoma patient: A case report. *Indian J Child Health*. 2018; 5(6):447-449.

Doi: 10.32677/IJCH.2018.v05.i06.013