High-risk Neuroblastoma in Young Adult and Long Term Survival with Multimodal Therapy: A Case Report

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Abstract

Objective: To present a case of high-risk, stage four neuroblastoma in a 20-year-old woman who survived more than 21 months with the multimodal therapy.

Methods: A case of high-risk, stage four neuroblastoma in a 20-year-old woman who survived more than 21 months with multimodal therapy is reported. The patient initially received neoadjuvant chemotherapy according to the Turkish Pediatric Oncology Group of Neuroblastoma, along with multiple doses of radiotherapy. After two cycles of induction chemotherapy, she successfully underwent tumor debulking surgery.

Results: With the multimodal therapy, patient remains in complete remission state and stable disease of the remaining lesions is observed in this patient.

Conclusions: Neuroblastoma is a rare disease in adults and associated with a high number of mortality. Early and accurate diagnosis and multimodality of treatments are important to achieve disease control. Long term follow up is necessary for such patients.

Keywords: High-risk Neuroblastoma, long term survival, young adult

Introduction

Neuroblastoma is an embryonal neoplasm of the sympathetic nervous system arising from the neural crest. The incidence of neuroblastoma peaks in infancy and childhood. Meanwhile, in adults, only one case in ten million populations was reported.[1] It has a unique clinical and biological heterogeneity of the tumors. Adolescent neuroblastoma often has a more indolent and chemo-resistant profile, associated with dismal survival.[2] The majority of neuroblastoma cases in adults showed high mortality within five years of follow-up.[3] There is no standard treatment protocol for adult neuroblastoma, and the treatment protocol still uses pediatric guidelines.[1] We present a rare case of high-risk neuroblastoma in 20-year-old women who had long-term disease stability and survival for more than 5 years with multimodal therapy.[4]

Case

A 20-year-old woman presented to our hospital with a one-month history of severe pain in the lump on her neck's left side. She lumped for the last eight years; it was not visible yet palpable at first and it had been slowly growing to approximately a grape-sized around six years ago. A histopathological finding from the left cervical lymph node performed six years ago revealed neuroblastoma, with immunohistochemical (IHC) staining positive

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Table Chemotherapy regimens on Turkish Pediatric Oncology Group Neuroblastoma 2003[1]

Chemotherapy	Drugs	Schedule
Induction cycles A3–1 cycle 15–19 July 2019	Vincristine	1.5 mg/m^2/day, D 1 and 5, IV push
	Ifosfamide	1.8 g/m^2/day, D 1-5, IV continues infusion
	Dacarbazine	250 mg/m^2/day, D 1-5, IV 30 min
	Adriamycin	20 mg/m^2/day, D 1-3, IV over 4 h
A5–1 cycle 15–19 August 2019	Cisplatin	30 mg/m^2/day, D 1-5, IV continues infusion
	Cyclophosphamide	300 mg/m^2/day, D 1-5, IV over 1 h
	Etoposide	150 mg/m^2/day, D 4 and 5, IV 1 h

for expression of *CD56*, chromogranin-A, and synaptophysin. Although she had been suffering from the lump for the last eight years (May 2014), she did not seek medical treatment. Instead, she preferred traditional medicine, dealing with herbal therapies.

She underwent twice positron emission tomography (PET), the first in 2016 and the second in 2017. The first PET showed 3.79 x 1.44 cm hypermetabolic multiple lymph nodes chains at the left superior jugular to left supraclavicular, and a hypermetabolic lesion at the body of the second thoracic vertebra, with the maximum standardized uptake values (SUV), was 27 (Fig. 1A, B). The second PET in 2017 showed advanced disease progression and a larger left neck soft tissue mass sized 9.3 cm x 8.4 cm x 10.0 cm with an SUV maximum

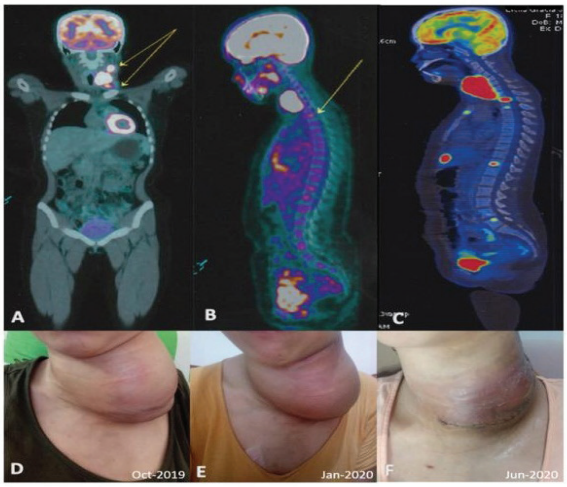

Fig. 1 (A-F): Coronal and axial views of patient's PET in 2014 (A and B); restaging PET showing progressive disease three years later (C). Clinical views after the first radiotherapy, revealed a left-sided neck mass sized 12 cm x 10 cm x 10 cm (D), after two cycles of temozolomide, sized 10 cm x 8 cm x 8cm (E), and after debulking surgery (F)

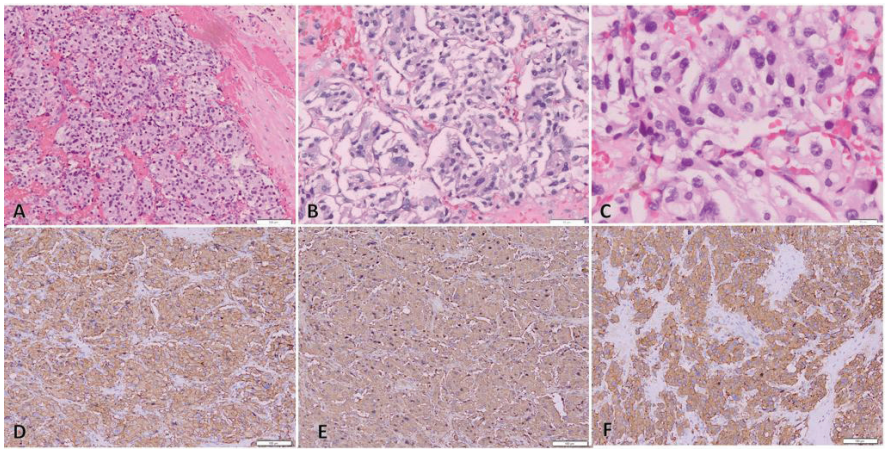

Fig. 2 (A-F). Hematoxylin and eosin (H&E) staining from tissue biopsy (A) 100x, (B)200x, and (C)400x, showing clusters and packets of small neoplastic cells forming Homer-Wright rosettes, with fairly dispersed chromatin, inconspicuous nucleoli, and indistinct cytoplasm. CD56 (D), chromogranin (E), and synaptophysin (F) IHC stains are positive in this tissue

score of 44.6 (Fig. 1C). Medially the mass slightly compresses the trachea lumen, with the suspect of thyroid gland infiltration; laterally compressing left submandibular gland; inferiorly extending into 2nd level thoracic inlet, posteriorly extending with 6-7th cervical – first thoracic vertebra. There were also diffuse metastatic foci, including supraclavicular and anterior mediastinum lymph nodes, pulmonary, liver, pancreas, and over axial to the appendicular skeleton.

Physical examination revealed approximately 10 cm x 15 cm x 8 cm mass on her left neck. The mass was firm, immobile, tender, and had a lobulated surface. There was venectation of the skin over the lump, chest, and abdominal wall. Other physical findings were unremarkable, and all laboratory results were within normal limits. The histopathologic examination and immunohistochemical staining, which confirmed the diagnosis of neuroblastoma, are shown in Fig. 2. The patient has been diagnosed with high-risk stage four neuroblastoma.

A neck CT was performed before chemotherapy began in June 2019, and showed a single, large, left neck tumor, size 12.67 cm x 10.68 cm x 10.42 cm, involving its adjacent tissues, multiple cervical lymphadenopathies, multiple bone destructions, and pulmonary metastases. Finally, in July 2019, the patient received a chemotherapy regimen according to the Turkish Pediatric Oncology Group of Neuroblastoma with one cycle of induction A3 and A5 (Table 1), along with zoledronic acid (4 mg intravenous, qd). After two cycles of induction chemotherapy, the tumor size reduced (Fig. 1D) and she had a stable disease. The therapy was followed by radiotherapy of 40 Gy in 20 daily fractions over four weeks. Waiting for debulking surgery, the patient received two cycles of temozolomide 200 mg/m^2/day (240 mg) per os (PO) for days 1–5, every 28 days (Fig. 1E). This treatment is based on research made by Zhu *et al*.[5] In June 2020, the patient underwent successful tumor debulking surgery (Fig. 1F). Afterward, the patient was started on 20 cycles of postoperative radiotherapy. The patient is under follow-up, after 21 months she is in complete remission of the primary neuroblastoma and stable disease of the base of the remaining lesion on clinical examination.

Discussion

Arising from primitive neural crest cells, neuroblastoma incidence peaks in infancy.[2] There are only <5% of neuroblastoma cases diagnosed after ten years of life. Even though older patients with neuroblastoma (>18 months) have a more indolent disease course, they are associated with poor prognosis.[6] Esiashvili *et al*. reported a 45.9% and 36.3% survival rate in adults (>20 years old) with neuroblastoma for three and five years, respectively.[7] Primary neuroblastoma could occur anywhere along all sympathetic nerve chains.[3] Moreover, head and neck neuroblastoma are rare but more common

in older age (>17 years old). A study by Kauffman *et al*.[1] reported only 3.9% out of 4.500 of their patients presented with head and neck neuroblastoma. Interestingly, they have a more favorable prognosis when compared with the other tumor locations. Neuroblastoma can be classified into low-risk, intermediate, and high-risk groups based on the patient's age at diagnosis, tumor stage, histopathology examination using The International Neuroblastoma Pathology Classification (INPC) system, deoxyribonucleic acid (DNA) index, and the presence of MYCN amplification.[2] According to the classification, our patient with 20 years of age at diagnosis and the stage-4 tumor is included in the high-risk group. Neuroblastoma is rare in adults, but it is important to consider it as one differential diagnosis from other small round blue cell tumors.[3] In our case, we consider lymphoma, small cell carcinoma, rhabdomyosarcoma, and primitive neuroectodermal tumor (PNET) as the differential diagnosis. It was subsequently excluded based on IHC findings: The lack of staining for lymphoid marks CD20, CD3, and CD30 rules out lymphoma, while lacking cytokeratin's expression (MNF116, Cam5.2) excludes small cell carcinoma. Furthermore, the absence of desmin staining rules out rhabdomyosarcoma, and the lack of CD99 expression argues against primitive neuroectodermal tumor (PNET) in favor of neuroblastoma.

The treatment regimens used for children with high-risk neuroblastoma have four main components: (1) induction chemotherapy, (2) local control, (3) consolidation, and (4) maintenance therapy.[2] Most currently employed induction regimens for high-risk neuroblastoma utilize a combination of anthracyclines, platinum-containing compounds, alkylating agents, and topoisomerase-II inhibitors. The most recently completed protocol for high-risk neuroblastoma treatment employed by the Children's Oncology Group (COG) utilized six cycles of induction chemotherapy, including the combination of topotecan and cyclophosphamide for the first two induction cycles, cisplatin, and etoposide for cycles 3 and 5 and cyclophosphamide, vincristine and doxorubicin for cycles 4 and 6.[8] European protocols have utilized COJEC/ OPEC regimens, which include cisplatin (C), vincristine (O), carboplatin (J), etoposide (E), and cyclophosphamide (C) or vincristine (O), cisplatin (P), etoposide (E), and cyclophosphamide (C). In a recent study, a regimen using 'rapid' COJEC aiming to increase treatment dose intensity was evaluated. Rapid COJEC was administered in 8 cycles, separated by ten-day intervals, allowing completion of induction within 70 days from administering the first drug. Rapid COJEC has been incorporated into the standard treatment regimen for these children with high-risk neuroblastoma.[9] Myeloablative chemotherapy with autologous stem cell rescue (ASCR) is recommended for consolidation therapy.[2,10]

Local control is a critical component of high-risk neuroblastoma therapy to prevent the local recurrence of the disease. Local control treatment modalities include surgical resection, generally after 4–6 cycles of induction therapy, external beam radiation to the primary site, and other active, residual disease sites.[2] Radiotherapy was recommended for the primary and all bulky metastasis following induction chemotherapy and surgery, and the total dose was modulated by age (25 Gy ≤ 2 years and 35 Gy > 2 years).[11] Patients with high-risk neuroblastoma typically enter the maintenance phase of therapy after induction chemotherapy, surgical resection, myeloablative therapy with ASCR, and radiation therapy.[2]

Our patient received two cycles of induction chemotherapy according to the Turkish Pediatric Oncology Group Neuroblastoma 2003 regimen: induction A3: vincristine, ifosfamide, dacarbazine, adriamycin for five days and A5: cisplatin, cyclophosphamide, etoposide for five days.[11] We chose this regimen because of the availability of drugs in our hospital. She had a stable disease after two cycles of chemotherapy. We did not continue with myeloablative therapy with autologous stem cell rescue because of toxicity and limited hospital resources. She received local control with external beam radiotherapy. After radiotherapy, we give her temozolomide. Temozolomide was considered because of the tendency of mass enlargement after radiotherapy. Temozolomide has been recommended for second-line chemotherapy for neuroblastoma either as a single agent or combined with topotecan or irinotecan, or etoposide. This temozolomide-based regimen has a response rate of around 47% to 73%.[12]

Patients with high-risk neuroblastoma who do not respond to induction therapy are more difficult subgroups to treat, with long-term survival rates of less than 20%.[2] Tumor response rates are also lower in adolescents and adults, who often have indolent, chemoresistance tumors compared to tumors

in younger children that tend to be more responsive to chemotherapy.[6] However, our patient has a stable disease and a reduction in tumor size after induction chemotherapy, radiotherapy, and temozolomide. The successful neoadjuvant therapy makes debulking surgery possible in our patients. With multimodality treatment, our patient survives for more than five years with stable disease.

Neuroblastoma has to be considered a differential diagnosis of neck lump despite its rare incidence in adolescents. Early and accurate histopathology examination has an important role in confirming the diagnosis. Regarding the chemo-resistant profile of neuroblastoma in adolescents, early and multimodality treatments are important to achieve disease control.

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