Case Report *Olgu Sunumu*

Adult pelvic neuroblastoma: long-term survival and review of the literature

Erişkinlerde pelvic nöroblastom: Uzun dönem sağkalım ve literatürün gözden geçirilmesi

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Abstract

Here, we report a 52-year-old man with pelvic neuroblastoma; to our knowledge, he is the oldest patient reported in the literature. A large retroperitoneal pelvic tumor was located between the bladder and rectum without any invasion to the adjacent organs. A 24-hour urine catecholamine examination revealed that vanillin mandelic acid excretion was above the normal range. The tumor was resected without any pelvic organ injuries. Histopathology showed pleomorphic cells with spindle-shaped vesicular nuclei. The immunostaining results for NB84, bcl-2, neuron-specific enolase, and CD56 were positive. CD99 showed weak cytoplasmic staining, which is consistent with a primitive neural or neuroectodermal-type neoplasm. However, NB84 positivity and an intact Ewing sarcoma gene locus (EWS) locus using fluorescence in situ hybridization analysis implied neuroblastoma. Appropriate immunohistochemical studies distinguished adult neuroblastoma from other differential diagnoses, especially primitive neuroectodermal tumor. Despite the low stage of the tumor, the patient's age and the large size of the tumor necessitated 6 cycles of adjuvant combination chemotherapy. Radiotherapy was not indicated for the patient, but he was followed regularly by pelvic computed tomography. This patient has benefited from a tumor-free survival for up to 6 years. Neuroblastoma is a differential diagnosis in patients with a pelvic mass, and treatment may be given according to pediatric protocols.

Key words: Adult neuroblastoma; NB84; neuroblastoma staging systems; pelvic mass; survival.

Özet

Burada, bildiğimiz kadarıyla literatürde bildirilen en yaşlı vaka olan 52 yaşında pelvik nöroblastomu olan erkek hastayı sunuyoruz. Hastada mesane ve rektum arasında çevre organlara yayılımı olmayan büyük bir retroperitoneal pelvik tümör mevcuttu. İdrarda 24-saatlik katekolamin değerlendirmesinde vanilin mandelik asit atılımı normal sınırın üzerinde idi. Tümör herhangi bir pelvik organ hasarı olmaksızın çıkarıldı. Histopatolojik değerlendirmede iğ-şekilli veziküler nükleusu olan pleomorfik hücreler görüldü. NB84, bcl-2, nöron-spesifik enolaz, ve CD56 için immünboyama sonuçları pozitif idi. Primitif nöral veya nöroektodermal tip tümörler ile uyumlu olarak CD99 zayıf sitoplazmik boyama gösterdi. Ancak, NB84 pozitifliği ve floresan in situ hibridizasyon analizi kullanılarak elde edilen *intact* Ewing sarkomu gen lokusü nöroblastomayı düşündürdü. Uygun histokimyasal çalışmalar yetişkin nöroblastomayı diğer ayırıcı tanılardan, özellikle primitif nöroektodermal tümörden ayırmaktadır. Tümörün düşük evresi, hastanın yaşı ve büyük tümör boyutu, 6 kür adjuvan kombine kemoterapi gerektirmiştir. Radyoterapi endikasyonu yoktur, ancak hasta düzenli olarak pelvik bilgisayarlı tomografi ile izlenmiştir. Hastanın 6 yıla kadar tümörsüz sağkalım avantajı olmuştur. Pelvik kitlesi olan hastalarda nöroblastom ayırıcı tanıda düşünülmelidir ve tedavi pediatrik protokoller göre verilebilir.

Anahtar sözcükler: NB84; nöroblastom evreleme sistemleri; pelvik kitle; sağkalım; yetişkin nöroblastomu.

Submitted (Geliş tarihi): 15.05.2010 *Accepted after revision (Düzeltme sonrası kabul tarihi):* 22.07.2010

Neuroblastoma, which is a neural crest cell-derived tumor, rarely occurs in adulthood, but it is one of the most common solid tumors in children. Less than 10% of patients are older than 10 years.[1,2] Pelvic neuroblastoma is an unusual tumor (5% of all neuroblastoma types) with a much more favorable prognosis than abdominal neuroblastoma. Several cases of malignant pheochromocytoma of the urinary bladder have been reported, but few cases of adult pelvic neuroblastoma have been reported in the literature.[3-5]

Currently, there is no standard treatment guideline for adult-onset neuroblastoma. Despite treatment with standard children's protocols, adult survival is poor, especially patients with localized disease have a more aggressive course than children.[6]

Surgical resection of pelvic neuroblastoma is a technical challenge, but the complete removal of the tumor plays a major prognostic role in localized treatment.[6]

When an adult presents with a large solid pelvic mass, neuroblastoma should be considered as a part of the differential diagnosis, although this diagnosis is ultimately rare. If neuroblastoma is confirmed, tissues should be evaluated using histopathological examination in accordance with the International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Risk Group Staging System (INRGSS).[7]

To the best of our knowledge, our case of pelvic neuroblastoma is the oldest patient reported in the literature who has presented with a pelvic mass that was treated using a complete en-bloc resection and adjuvant chemotherapy.

Case report

A 52-year-old man was admitted to our general hospital in April 2004 complaining of recent night sweats and low back pain in the sacrum that radiated to the back of thighs. He had a history of diabetes mellitus with initiation of occasional dysuria, constipation and a 7 kg weight loss over 2 years. Physical examination was normal except for a palpable pelvic mass during abdomino-pelvic and digital rectal examinations. Laboratory tests, including prostate spesific antigen (PSA), lactate dehydrogenase (LDH), routine hematological tests, and blood chemistry, were normal except for microscopic hematuria.

Pelvic and abdominal ultrasonography depicted a solid, heterogeneous, lobulated, and calcified mass that was 187×145×104 mm. Barium enema was normal except for an inferolateral shift of the colon. Voiding cystourethrogram confirmed the displacement of the bladder and urethral elongation. An abdominopelvic computed tomography (CT) confirmed that a pelvic tumor was located between the bladder and rectum, which displaced the bladder to the right side; no tumor invasion or abnormal abdominopelvic lymph nodes were observed (Fig. 1a).

Bone marrow biopsy showed no evidence of metastatic disease, and a whole-body metaiodobenzylguanidine (MIBG) diagnostic scan was also normal. The 24-hour urine catecholamine examination showed that vanillin mandelic acid (VMA) was over the normal range (23 mg, normal range 0.5-12 mg).

Under general anesthesia, a retroperitoneal pelvic tumor was observed through a lower midline abdominal incision. The tumor was resected from the bladder and prostate without any invasion into adjacent organs during a 5-hour operation. An examination of the fresh frozen specimen examination revealed that resected margins were tumor-free without abnormal pelvic lymph nodes (Fig. 1b).

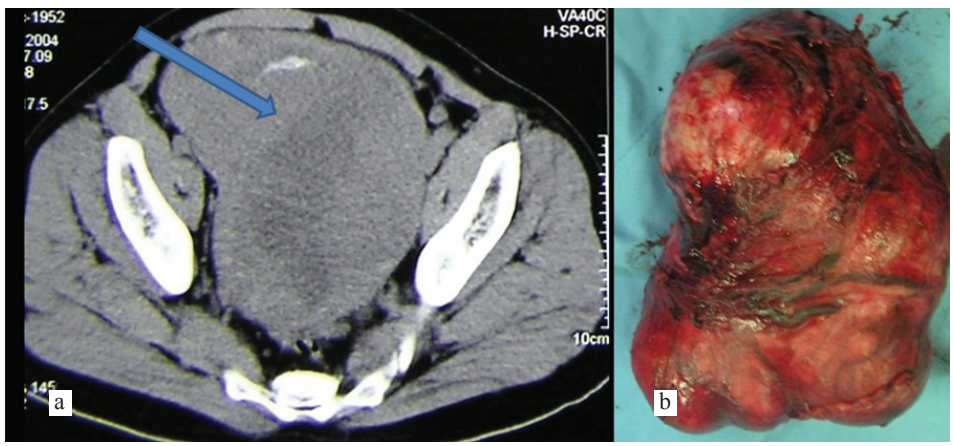

Figure 1 (a) Abdominopelvic computed tomography confirmed the ultrasonography findings of no tumor invasion to the pelvic wall and no abnormal lymph nodes in the abdomen or pelvis (arrow). (b) The mass was completely resected intact without any pelvic organ injury or residual tumor.

The postoperative urine VMA levels were reduced to 12.9 mg after 2 days. Primary histological examination of the resected tumor showed a neurological differentiation. Both primitive neuroectoderm and sympathicoblastoma were proposed as diagnoses.

The patient was referred to the Sarcoma Unit, Royal Marsden Hospital, London, England, for a second opinion and further management. A histological review of tumor sections showed a cellular neoplasm that was composed of pleomorphic cells with spindle-shaped vesicular nuclei. Many cells showed indented nuclei and an abundant fibrillary matrix with a rosette pattern, which is consistent with a neurological differentiation. Immunostaining results for NB84, bcl-2, neuron-specific enolase (NSE) and CD56 were positive. CD99 showed weak cytoplasmic positivity, and smooth muscle actin (SMA), desmin, synaptophysin, chromogranin, S100 protein, cytokeratin AE1/AE3, CD45, CD34, CD117, calretinin, calponin, β-catenin, epithelial membrane antigen (EMA), and Cam5.2 were all negative. Reticulin showed a nested pattern. This was not a germ cell tumor histopathologically, and the markers were not typical for Ewing's family tumors. These primitive neural or neuroectodermal neoplasmic features coupled with NB84 positivity implied a neuroblastoma (Fig. 2). Based on the INRGSS factors in this patient, the MYCN status was not amplified because 11q and 1p were normal.

The patient received 6 cycles of vincristine 2 mg, dacarbazine 600 mg/m^2 per day on days 1 and 2, and cyclophosphamide 800 mg/m^2 on day 1. The vincristine and dacarbazine regimen was repeated 4 additional times every 3 weeks.

Discussion

To the best of our knowledge, this patient is one of the oldest patients with neuroblastoma. There has been a steady decline in the incidence of adult neuroblastoma from 0.47 cases per million per year in 1973-1977 to 0.12 cases per million per year in 1998-2002.[4] Adults with neuroblastoma have a significantly worse outcome than children. This may

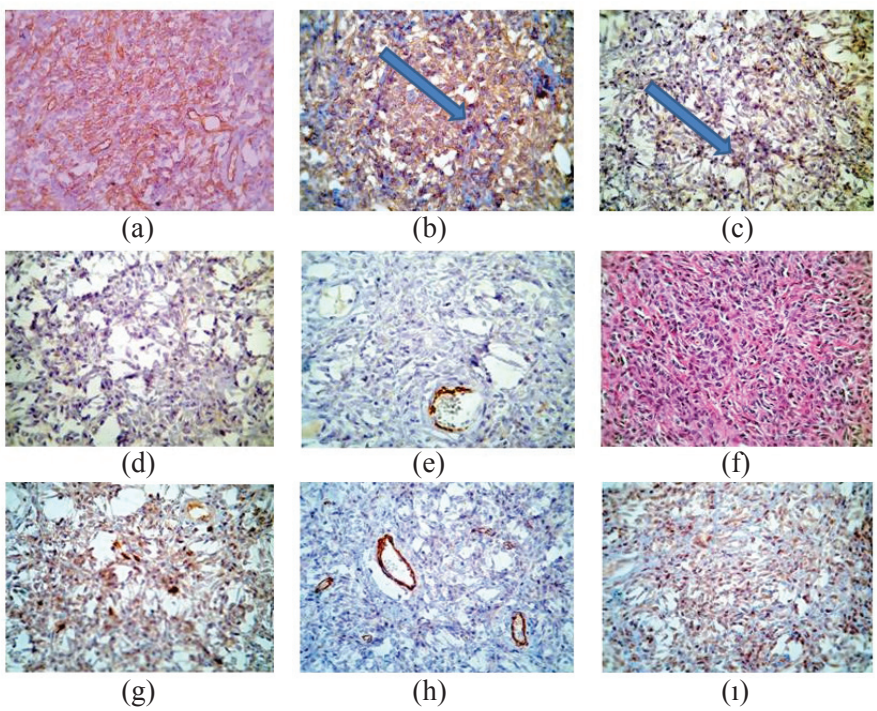

Figure 1 Hematoxylin-eosin stain and immunohistochemical analysis of neuroblastoma (×400). (a) CD34 negative, (b) CD99 showed weak cytoplasmic positivity (arrow), (c) NB84, cells in the specimen were stained brown diffusely (arrow), (d) cytokeratin AE1/AE3 negative, (e) desmin negative, (f) hematoxylin-eosin, (g) S-100 negative, (h) SMA negative, (ı) synaptophysin negative.

be due to tumor biology, a more virulent clinical course, or the fact that adults are less sensitive or have poor tolerance to pediatric chemotherapy regimens. Neuroblastoma is diagnosed more frequently in advanced stages in adolescence and has common sites of metastases compared to children.[5]

The observed 3- and 5-year survival rates were the lowest among adults (45.9% and 36.3%, respectively), but 86% and 84.6% of infants survived for 3 and 5 years. A long-term evaluation of adult neuroblastoma survival in a 10-year follow-up study revealed a continuous decrease in survival during the first 7 years after diagnosis.[5]

Although the location of the tumor (pelvic), negative chromogranin, and synaptophysin make the diagnosis of neuroblastoma controversial, other differential diagnoses, such as a sarcoma with neuroectodermal differentiation, was not ruled out.

Because CD99 showed weak cytoplasmic positivity, Fluorescent In Situ Hybridization (FISH) analysis was performed to investigate the presence of Ewing sarcoma gene locus (EWS) translocation, which suggests Primitive Neuroectodermal Tumors (PNET)[8] as a differential diagnosis. However, FISH analysis showed an intact EWS locus. The undifferentiated subtype had ultrastructural features with the neurological characteristics of neuroblastoma and lacked a chimeric transcript (EWS-FLI1 or ERG) that is specific for PNET.

Based on histopathological studies, the patient's condition, and genetic characteristics, the tumor could be classified as an INSS stage 1 tumor. Although surgery alone is sufficient for stage1 neuroblastoma, and chemotherapy is not highly recommended in this stage, microscopic disease may remain after surgery. Furthermore, tumor size suggests an "advanced-stage" status in other staging systems.[9] The frequent late local and regional recurrences that are seen in these adult tumors compared to pediatric tumors should also be considered. As a result of all of these reasons, and because chemotherapy may benefit individual patients especially when there have been very few treated patients reported in the literature with adult-onset neuroblastoma, we decided to perform primary chemotherapy in this patient. Nevertheless, a negative whole-body scan and a lack of the usual indications for radiotherapy for localized, inoperable primary or painful metastases convinced us that radiotherapy was unnecessary. We monitored the patient closely using regular imaging to identify any early recurrence of tumor using a whole-body MIBG diagnostic scan and a whole-body indium-111 octreotide scan. If the disease recurred despite adjuvant treatment, one should investigate whether the tumor concentrated MIGB or somatostatin analogues, and the tumor might be susceptible to targeted radioisotope therapy. These investigations have remained negative 6 years after the initial surgery.

As a conclusion, neuroblastoma should be considered in almost all cases of abdominopelvic masses, although its incidence is rare in adulthood. Moreover, if a pathological examination confirms a diagnosis of neuroblastoma, treatment may be performed based on pediatric guidelines because there are no principles for the treatment of adult-onset neuroblastoma. Surgical resection of the tumor followed by chemotherapy provided a satisfactory long-term survival in our adult neuroblastoma case. However, adult patients need regular follow-up investigations because of the frequent recurrence of these tumors compared to pediatric tumors.

Conflict of interest

No conflict of interest was declared by the authors.

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doi:10.5152/tud.2011.032