

NEUROBLASTOMA IN AN ADULT: A CASE REPORT OF A RARE ENTITY WITH A SUMMARY REVIEW

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ABSTRACT

Neuroblastoma is a very uncommon neoplasm in adulthood. It occurs almost exclusively in children younger than ten years (More than 90% of cases). We report the case of a healthy 40-year-old male who complained of a right flank pain in 2010. Clinical examination revealed an enormous abdominal mass involving the adrenal gland as showed at abdominal CT scan. The patient underwent a surgical en-bloc excision of the right adrenal mass, after a laborious dissection of the tumor. Histological and immunohistochemical findings were suggestive of neuroblastoma. Adjuvant treatment was not indicated since the complete gross excision of the tumor was performed, and subsequently, the patient was considered stage 1 disease and because of the unavailability of MYCN status, necessary for achieving risk group stratification and a risk-adapted strategy. The patient remained in good local control, until January 2015 when he accused a locoregional and metastatic relapse consisting of two new para-renal masses and magma of celiac adenomegaly extending into the mediastinum. As the mass was considered unresectable, the therapeutic decision of administrating neoadjuvant chemotherapy, followed by local treatment (surgery and / or radiotherapy) based on tumor response was taken. Given the bad tumor response to systemic treatment, a palliative radiotherapy was instaured. Currently, the patient is two months after the end of radiation with mild clinical improvement. The purpose of presenting this case is not only to report an uncommon malignancy in adulthood but also to raise awareness among clinicians adding this clinical entity as a differential diagnosis when a retroperitoneal mass is identified. We also conducted a literature review to enhance clinicians' acknowledgment about the management of this rare entity in adults.

KEYWORDS Neuroblastoma, Adult, retroperitoneal mass

Introduction

Neuroblastoma is a very uncommon neoplasm in adult life. In fact, it is almost exclusively a disease of childhood where it holds the third rank. More than 90% of cases occur in patients younger than ten years[1, 2].

Only 1 case per 10 million adults per year is diagnosed whereas the incidence reaches 1 case per 100,000 children per year [3-5]. According to the Rabat cancer registry of Morocco, only five children with neuroblastoma have been registered between 2005 and 2008, that is to say, an incidence of 2 new cases per one million children per year, whereas no adult case has been registered in the same period[6, 7].

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We try to clarify this extremely rare pathology through the report of a medical observation of an unusual case of neuroblastoma in an adult man with a literature review.

Case Report

A 40-year-old male with no significant medical history experienced few months before medical consultation in March 2010 a right flank pain.

Clinical examination revealed an enormous abdominal mass of the right side in a patient with good performance status (ECOG=1).

An abdominal CT scan showed a large hypodense and heterogeneous retroperitoneal mass depending on the right adrenal gland, well demarcated, measuring 14x12.5x3 cm, without evidence of adjacent structures involvement.

Surgical exploration found an enormous right adrenal mass, reaching the diaphragm, and displacing liver, colon, right kidney and the inferior vena cava. The patient underwent an en-bloc excision of the right adrenal mass, after a laborious dissection of the tumor. The postoperative course was simple without uncommon complication.

Pathologic examination revealed a high-density proliferation, consisting of broad diffuse layers of small, round, blue cells. The cells have hyperchromatic nuclei and form rosettes. This spread is surrounded by a thick capsule and appears to arise from the adrenal medulla (Fig 1). These findings strongly evoked neuroblastoma.

Immunohistochemical (IHC) staining confirmed the diagnosis since it was diffuse and strongly positive for S100 and NSE.

Adjuvant treatment was not indicated since the complete gross excision of the tumor was achieved, and the patient was considered stage 1 disease. Furthermore, because of the unavailability of MYCN status, we could not establish risk group stratification and a risk-adapted strategy.

The patient remained in good local control, until January 2015 when he accused the same symptomatology. New radiological assessments, consisting of the chest, abdominopelvic and bone CT-scan objectified retroperitoneal recurrence as two new para-renal masses and magma of celiac adenomegaly extending into the mediastinum (Fig 2).

No bone, liver or pulmonary focal lesion was detected. A new surgical biopsy revealed a differentiated neuroblastoma. This mass was judged unresectable.

The patient was proposed to neoadjuvant chemotherapy, followed by local treatment (surgery and / or radiotherapy) based on the tumor response. The patient received four courses of etoposide and carboplatin-based chemotherapy. Given the bad tumor response to this regimen and the risk of progression, we decided to make a palliative radiotherapy. So, the patient underwent an external beam conformal radiotherapy, focused on the lesion by two diverging beams, with a total dose of 30 Gy in 2 Gy/fraction over three weeks (Fig 3). Radiation therapy was well tolerated with no acute toxicity noted.

Currently, the patient is two months after the end of radiation with mild clinical improvement. CT scan is planned for three months, to detect an eventual tumor progression requiring second-line chemotherapy.

Discussion

We report a rare case of neuroblastoma in an adult patient. Neuroblastoma arises from primitive sympathetic neural cells

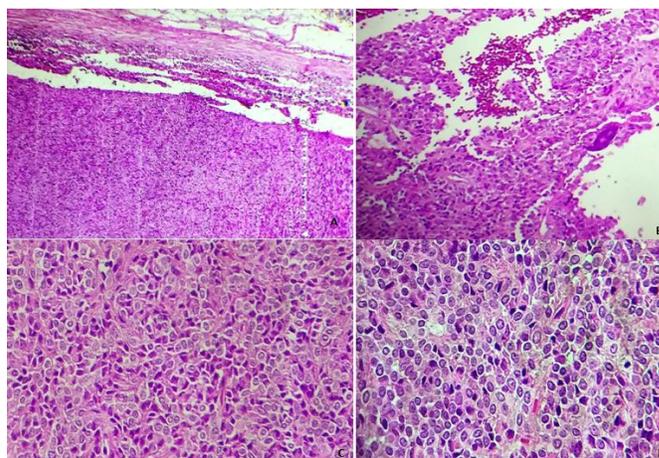


Figure 1: A) Encapsulated tumor composed of cellular diffuse sheets (HEx4), B) Few pseudo-rosettes structures were noted (HEx10), C) Small round cell tumor with dusty chromatin and fine nucleoli (HEX20), D) Tumor cells form rosettes images and show mitotic figures.



Figure 2: Abdominal CT scan showing para-renal masses and magma of celiac adenomegalies extending into the mediastinum.

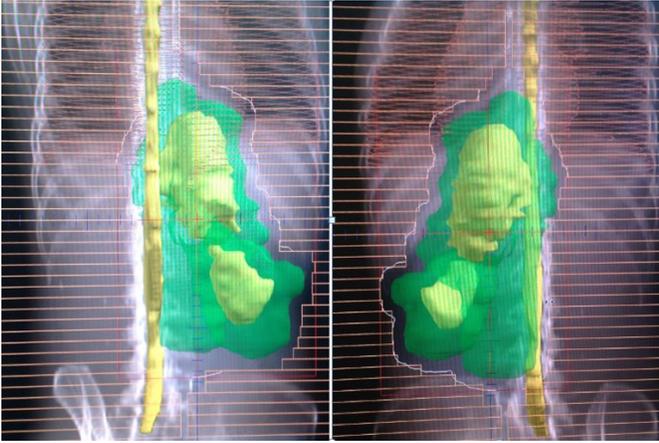


Figure 3: External beam conformal radiotherapy targeting the retroperitoneal mass and regional lymph nodes by two oblique beams.

primarily in the adrenal medulla. It can also occur from the paraspinal sympathetic ganglia mainly in the abdomen and pelvis, less frequently in the thorax, head or neck, and extremities [3, 8]. Most of the literature data consist of case reports and retrospective series, but no clinical trial of such unusual adult malignancy is currently available in adult patients [3]. Because of the rarity of this malignancy in adulthood, staging systems and risk assessment tools as well as treatment regimens and protocols have been inspired by pediatric data [3]. Table (1) summarizes existing reports of adult neuroblastoma available in the literature between 1990 and 2015 [1-4, 9-17].

Symptoms are numerous, and most of them are nonspecific. They depend on primary tumor location and its possible metastatic extent. Most frequently, the primary site is the abdomen (two-thirds of children) manifested by palpable mass, digestive problems, discomfort, fullness, pain or rarely intestinal obstruction. Sometimes, it can be completely asymptomatic[18]. A comparison of primary site location between adults and children was not possible in the report of the SEER database, because of constraints of the data[4]. Mediastinal extent may be associated with respiratory symptoms related to the compression of the trachea with resulting stridor, or symptoms related to the compression of superior vena cava. These manifestations are usually associated with large thoracic tumors, whereas most of the small primary thoracic tumors are detected incidentally on radiographs during evaluation of other complaints.

Our patient complained of abdominal and lumbar pain without any thoracic symptoms even in the presence of extensive, but noncompressive, mediastinal mass.

Confirmation of diagnosis is made by a biopsy of the primary tumor. Also, the catecholamine metabolites assay can be useful for initial diagnosis and monitoring of disease activity. However, very few tumors secrete catecholamines in adulthood (40–57% of adults compared to 95% of children with neuroblastoma)[19].

Metastatic disease at diagnosis was noted in approximately one-third of all adult neuroblastoma patients[4]. Neuroblastoma metastasizes by both lymphatic and hematogenous routes. Regional lymph node involvement is found in 35% of cases with localized disease. Involvement of lymph nodes outside the cavity or region of origin is considered as a disseminated disease[18]. Since lymph node dissection has not been performed in our patient an adequate staging was missed.

Most frequent metastatic sites are bone, bone marrow, liver,

and skin. Whereas metastatic extension to the lung and brain parenchyma is most often associated with recurrence or end-stage disease[20].

A full assessment is required before starting treatment. The minimum requirements for staging include abdominal imaging by CT scan and/or MRI, which are necessary to localize the tumor accurately, to provide information about tumor size and involvement of adjacent organs. Chest CT is needed if the chest radiograph is positive or if abdominal mass or lymph node disease extent into the chest, as in our patient's case. Brain CT scan should be regarded as suggested by clinical symptoms. Bone radiographs and either technetium radionuclide scan or meta-IOD benzyl guanidine (MIBG) scintigraphy may be useful for detection of distant metastases. MIBG is preferred to technetium scan, given its higher sensitivity and specificity. In fact, MIBG scan highlights the fixation of the radiopharmaceutical in the primary mass and the increased drug concentration at the metastatic site. Bilateral iliac crest bone marrow aspirate and biopsy are required to detect microscopic tumor involvement[9]. Currently, the patient experiences a metastatic relapse consisting of mediastinal lymph nodes, whereas the achieved imaging studies did not find any other metastatic site.

Several prognostic factors have been considered for children. However, given the rarity of this disease in adults, there are no prospective data examining these prognostic factors in adulthood. In fact, the outcome of patients with neuroblastoma depends on both tumor and patient characteristics, including age at diagnosis, stage of disease, especially extent and site of metastases, histological differentiation, mitosis-index, and cytogenetic features of MYCN amplification, DNA ploidy, and chromosomal aberrations.

In most series, neuroblastoma in adults rarely expresses MYCN amplification [2, 4]. The prognostic significance of MYCN amplification was illustrated by several studies in the pediatric population. Patients with MYCN-amplified tumors had a significantly worse event-free and overall survival compared to those without this structural abnormality[21, 22]. Furthermore, regardless of patient's age and stage of disease, amplified expression of MYCN oncogene is the worst paraclinical prognostic factor. Identification of MYCN status was suggested to our patient, but could not be done given the lack of technical and financial resources.

These prognostic factors are so much important as they determine the risk-assignment necessary for the choice of the treatment protocol. In fact, different treatments are recommended for various risk groups. In childhood, patients with high-risk disease following to the Children's Oncology Group Neuroblastoma Risk strata are those who are older than 18 months with disseminated disease or localized disease with unfavorable features such as MYCN amplification. Whereas, all adult patients can be considered at high-risk of death from disease regardless of the stage because of their age [23]. Currently, there are no standard treatment guidelines for treating adult neuroblastoma patients, but treatment protocols are inspired from pediatric population studies [4]. High-risk neuroblastoma requires induction chemotherapy followed by surgical resection of the primary if possible. Complete resection without any spillage of the tumor is strongly required, even if the importance of achieving gross total resection of the primary remains controversial[24, 25].

Adjuvant radiotherapy to the tumor bed and possibly other sites of bulky may be beneficial in preventing local tumor relapse. It may be a useful therapy for the control of local recurrence[26].

Authors	Number of cases	Ages(Year)	Institution (Period)	Outcome
Franks et al. (1997)[2]	16	13-33	University of California-San Francisco (1968–1995)	5- year OS= 44%
Kushner et al. (2003)[9]	30	12-41	The Memorial Sloan-Kettering center(1985-2001)	-17 died of disease (7-65 months) - 6 Alive with disease(11-130 months) -7 Not evidence of disease (9-181 months)
Esiashvili et al(2007)[4]	144	20 - 85	SEER database (1973-2002)	5- year OS=36.3%
Yapanoglu et al(2008)[10]	1	54	Ataturk University, TURKEY	Followed for 18 months without recurrence
Manchanda et al(2009)[1]	1	54	Institute of Dental Science & Research	Died during initial treatment
Miranda S. et al(2010)[11]	1	23	University of Montes Claros, Brazil.	Followed for 36 months with disease progression
Vénat-Bouvet et al(2010)[12]	1	25	CHU Dupuytren, Limoges, France	Followed for 8 years with multiple recurrences
Ohtakia et al(2011)[13]	1	64	National Cancer Center Hospital, Japan	Followed for 10 months with recurrence
Bin Abdullah et al (2012)[14]	1	25	Al Ameen medical college and hospital, India	Followed for 6 months without recurrence
Gupta et al(2013)[15]	1	47	Midnapore Medical College, India	Followed for 15 months with disease progression
Conter et al (2014)[3]	118	18-82	The M.D. Anderson Cancer Center (1994-2012)	5 year OS -L1 disease: 90% -L2 disease:73% -M disease:13%
Imvrios et al(2014)[16]	1	26	University Medical School, Greece	No available follow-up
Lokesh et al (2015) [17]	1	22	Kidwai Memorial Institute of Oncology, India	Followed for 12 months without recurrence

Table 1: Review of Existing Reports of Adult Neuroblastoma (1990-2015).

Radiation therapy can also be an effective treatment modality, even in the metastatic setting, for obtaining a local control, especially in aggressive tumors with or without total resection of the primary [27]. Since surgery was not feasible after chemotherapy during the recurrence, we opted for definitive radiation therapy as the optimal treatment option for obtaining local control in our patient.

Consolidation by high-dose chemotherapy and autologous stem-cell rescue (HDCSR) is indicated for patients with good responsiveness. It improved event-free, and overall survival in high-risk pediatric patients through a meta-analysis of 3 randomized controlled trials enrolling 739 patients[28]. Even with HDCSR, most adult patients with neuroblastoma suffer from multiple recurrences and ultimate death from the disease[4].

Data about the role of HDCSR in the treatment of adult neuroblastoma are lacking and often contradictory. In fact, in a large series of 118 adult patients with neuroblastoma and 112 pediatric patients treated in the MD Anderson cancer center, only one adult M-stage disease (Distant metastatic disease) versus 45 of the same pediatric stage have been addressed with HDCSR[3]. Moreover, outcome (PFS and OS) of this group of patients was not statistically different from those treated without HDCSR. Since the authors failed to demonstrate any benefit from such aggressive therapy in adult patients, they do not recommend it as part of their protocol treatment [3]. Results from this large adult series conclude that, for adult patients with L1 disease (according to the INRG risk assessment system), combined surgical resection and RT seem likely to offer better PFS and OS than surgical resection or RT alone. However, adjunction of chemotherapy was not associated with any improvement in outcomes for both L1 and L2 stages or in local salvage treatment[3]. Similar results were found by the report of the Memorial Sloan-Kettering experience where chemotherapy in standard doses had only healing effect. However, high-dose chemotherapy combined with surgery and immunotherapy provided a higher response rate[9].

Historically, most of the literature data support that adults with neuroblastoma have significantly worse outcome than children. In fact, overall adult survival at five years does not exceed 36%, whereas it is about 85% in childhood [3, 4]. However, current survival rates remain very low in high-risk children (40%), even with an aggressive multimodality approach. These rates are similar to those found in adult, which in somewhere could explain the consideration of all adult patients as at high-risk disease. Many Hypotheses have been advanced to explain that fact: this may be due to tumor biology, higher incidence of unfavorable histologies and worse clinical course observed in adult patients, reduced tolerance to pediatric chemotherapy regimens or less sensitivity to these regimens [3, 9]. However, in the recent MD Anderson cancer center report, a similar survival outcome between the two patient populations has been found for all stage-matched categories[3]. The 5-year overall survival was 90%, 73% and 13% for stages L1, L2, and M respectively in adult patients[3]. Moreover, a long-term survival has been reported even with multiple recurrences during disease [3, 12].

Conclusion

The addition of our case to the literature offers new clinicopathological data useful for better defining the diagnosis and biological behavior of neuroblastoma. The purpose of presenting this case is not only to report an uncommon tumor in adulthood but also to raise awareness among clinicians adding this clinical

entity as a differential diagnosis when a retroperitoneal mass is identified. These tumors often have peculiar features and behave differently than those in infants and children. They present at an advanced stage, may have an aggressive course and a worse prognosis. Adjuvant chemotherapy and local radiotherapy should be considered even in early stage disease in adults due to their aggressive nature. Maximizing the intensity of therapy with stem cell rescue and identifying the best chemotherapy regimen are two directions of research. Comparison between single Vs tandem transplant is also under study. Further prospective studies are needed to assess whether pediatric regimens are active in adulthood and to identify biological behaviors of this tumor with resolving differences between pediatric variants.

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Competing Interests

The authors declare no conflict of interest.

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