Original article

Gonadal metastases in neuroblastoma: A Sequel of prolonged chemotherapy?

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A B S T R A C T

Background: A large majority of neuroblastoma continue to present with advanced disease with widespread dissemination. However, metastasis to the ovary or testis is infrequent with sparse literature even from the major neuroblastoma study groups. The aim of this study was to determine the group of patients in whom such a rare entity has occurred and evaluate any common factor and clinical implication.

Materials and methods: We retrieved records of all patients with abdominal neuroblastoma operated from January 2008 to August 2013. We selected the cases with overt gonadal (ovarian or testicular) metastasis at presentation or relapse and noted the details.

Results: Of the 186 cases of neuroblastoma four patients were having metastasis to the gonads (testis = 2, ovary = 2). All the four cases had extensive abdominal disease and received prolonged chemotherapy before the institution of local surgical treatment.

Conclusion: Protracted chemotherapy without timely and adequate local treatment may contribute to the metastases seen in unusual sites such as the gonads. However, the therapeutic implication of identifying gonadal metastases is uncertain in patients already having disseminated disease.

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1. Introduction

Neuroblastoma is a disease with some unique tumor biology and behavior. It has been extensively studied over the past several decades. However, it continues to frustrate the clinician, while at the same time, equally fascinate the tumor biologist. Even today more than 40% of children with neuroblastoma present with disseminated disease and represent a poor prognostic group [1]. Despite so many cases presenting with widespread metastases, overt involvement of the gonads is very rare. Only a couple of series have evaluated metastasis to the testis and a few reports have noted the ovarian involvement in neuroblastoma [2–5].

The purpose of this study was to review the cases of neuroblastoma at our institution, which had gonadal metastasis (ovarian or testicular) at presentation or relapse, and examine the common link, if any, in all these cases and evaluate the therapeutic implications.

2. Materials and methods

This was a retrospective study wherein we retrieved the data of all the cases of neuroblastoma that had undergone surgical excision in our institution from January 2008 to August 2013. We selectively recorded and examined the details of those patients who had an ovarian or a testicular metastasis either at presentation or during relapse.

3. Results

One hundred and eighty six cases of neuroblastoma had undergone surgical excision during the period. Four patients were noted to have overt gonadal metastasis. Two of them had metastasis at presentation and other two had it at relapse.

Case 1 A 17-month-old girl with abdominal neuroblastoma diagnosed elsewhere at the age of seven months had received
suboptimal chemotherapy for 10 months with no local treatment for the primary disease. At presentation in our institute, investigations revealed a large retroperitoneal tumor with bone marrow involvement by metastatic tumor; however, N-myc was not amplified. As the child had already received extensive chemotherapy, she was offered surgical excision. At surgery, along with bulky abdominal disease infiltrating the psoas muscle, synchronous metastasis in the right ovary was noted. A gross total resection of the tumor was performed along with oophorectomy. Child also received post-operative radiotherapy (RT). Seven months after completion of treatment, the disease relapsed at multiple sites including the bones and subdural deposit. The patient expired 24 months from the diagnosis of disease.

Case 2 A 9-year-old boy diagnosed with abdominal neuroblastoma had undergone a partial surgical excision followed by protracted chemotherapy and radiotherapy elsewhere. He was referred after 3 years of diagnosis, with disease progression for further management. At presentation, the patient had a large 15 × 15 cm retroperitoneal mass. Metastatic work-up did not reveal any metastasis. However, there was amplification of the N-myc gene. The child received 2 cycles of salvage chemotherapy and then underwent gross total resection of the abdominal tumor. After 6 months of completion of the treatment, the child was noted to have enlargement of the left testis and investigations revealed metastatic deposits in it along with the liver and lungs (Fig. 1A). The bulky left testis (Fig. 2A) causing discomfort to the child was excised by an inguinal orchidectomy, which showed metastatic deposits of neuroblastoma. The cut end of the spermatic cord was free of tumor. However, the child had disease progression and died 48 months from the time of initial diagnosis.

Case 3 An 8-year-old boy diagnosed with abdominal neuroblastoma elsewhere, received prolonged courses of chemotherapy after an open biopsy. Investigations at our institute revealed a 12 × 10 cm retroperitoneal mass with bulky left testis. Bone marrow was infiltrated with neuroblastoma and N-myc was not amplified. Salvage chemotherapy yielded a very good partial response. Surgical excision with more than 95% resection of the tumor and orchidectomy was performed. The cut end of cord was free of tumor. The patient received autologous bone marrow transplant followed by six cycles of cis-retinoic acid. After 13 months of completion of treatment, the child developed brain metastasis, for which palliative radiotherapy was administered. Subsequently, the patient received oral metronomic therapy. The disease seemed to be stable and a meta-iodo-benzyl-guanidine (MIBG) scan done 7 months later did not show any abnormal uptake. Child is alive with a stable disease 40 months from the date of first diagnosis.

Case 4 A five-year-old girl diagnosed elsewhere with non-metastatic abdominal neuroblastoma and treated with prolonged courses of chemotherapy and suboptimal resection was referred to our institute one year later with residual abdominal disease. Evaluation revealed localized disease in the abdomen with no distant metastasis. Although, surgery was advised the parents refused surgery. The child was started on metronomic therapy but defaulted. At the age of 12 years, the patient presented with progressive increase in the abdominal mass along with pain. Imaging revealed the presence of a large abdomino-pelvic mass, deriving its blood supply from branches of the uterine artery with bilateral massive hydroureteronephrosis, and multiple retroperitoneal lymph nodes (Fig. 1B and C). However, there was no evidence of metastatic disease in the remaining work-up. Following bilateral ureteral stenting for obstruction, the patient received salvage chemotherapy and underwent surgery. At surgery, the large abdomino-pelvic mass was in fact metastatic left ovarian tumor (Fig. 2B). Debulking along with salpingo-oophorectomy was performed. The patient is well 2 months after surgery and is receiving maintenance chemotherapy.

4. Discussion

Neuroblastoma is the most common extracranial solid tumor in children. According to the International Neuroblastoma Staging System (INSS), metastatic neuroblastoma is classified as stage 4 or 4S [6]. Common metastatic sites are bone marrow, skin, bone, the liver, and lymph nodes [2]. Gonadal involvement in neuroblastoma has been documented rarely. Testis as a sanctuary in leukemia and lymphomas is well recognized. However, testicular metastasis in solid tumors is a less common. Despite the fact that neuroblastoma presents with wide spread tumor dissemination, metastasis to gonads appears to be a rare event in neuroblastoma, as evidence by
the scarcity of reports in the literature [2–5,7]. While reviewing metastatic sites of neuroblastoma in patients referred to Memorial Sloan-Kettering Cancer Center (MSKCC) over a period of 25 years, Kushner et al. [3] found 11 cases of testicular involvement out of 289 male patients of abdominal neuroblastoma. Intrascrotal metastases were suspected in five of the 11 cases during life but only in two patients were biopsies attempted and confirmation made; the occult testicular involvement in the remaining six patients was discovered at autopsy. They concluded that the patients most likely to develop testicular metastasis were the ones with bulky infradiaphragmatic disease and bone and bone marrow involvement.

When records of German cooperative neuroblastoma treatment trials of a 20-year period were reviewed, Simon et al. [2] noted 15 patients with intrascrotal metastases in a series of 1076 male patients of neuroblastoma. Of these 15, 11 had paratesticular or testicular involvement at the time of presentation, three presented at disease relapse and one infant presented at progression of disease from Stage 4S to Stage 4. This study concluded that in patients with otherwise 4S disease, the isolated involvement of testis should not be taken into consideration to upstage them to stage 4.

The routes of spread to testis include hematogenous, lymphatic, retrograde through vas deferens and direct tumor extension from contiguous mass. In our cases it was not, a retrograde spread as in retrograde through vas deferens and direct tumor extension from diaphragmatic disease and bone and bone marrow involvement.

Ovarian involvement in neuroblastoma can occur in approximately 25% of the cases, although in the vast majority this has been an autopsy finding [8]. Clinically overt metastatic disease in the ovary has been reported by a very few authors [4,5,9]. In both our cases, metastatic ovarian tumor was an intraoperative finding. However, in the hindsight, the pelvic mass in case four reported to have vascular channels from uterine artery should have alerted us of the possibility of ovarian metastases.

The prognostic impact of gonadal involvement in neuroblastoma is unclear. Two patients had gonadal involvement at presentation and two had it during relapse. Common to all these cases was the fact that they were high-risk neuroblastoma and had received chemotherapy for a prolonged period without adequate and appropriately timed local treatment. Protracted chemotherapy may lead to resistant clones, which find a safe haven in uncommon sites like the gonads. All of them had bulky infradiaphragmatic disease; consistent with what has been reported in the earlier literature as the ones more likely to have gonadal metastases.

Conclusion

Gonadal metastases in neuroblastoma are infrequent. It is more often seen in patients with massive infradiaphragmatic disease. Protracted chemotherapy without timely and adequate local treatment may contribute to the metastases seen in unusual sites such as the gonads. In the patients with such a history of having received prolonged chemotherapy, after completion of the treatment, follow-up should include careful evaluation of the gonads as a possible site of relapse. However, the therapeutic implication of identifying gonadal metastases is uncertain in patients already having disseminated disease.

Conflict of interest

Nil.

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References