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Case Report
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Chronic Persistent Neuroblastoma, a Unique Presentation and Clinical Course in a Six-Year-Old Child: A Case Report

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Abstract

Neuroblastoma (NBL) is the most common intra abdominal childhood malignant tumor. NBL is a malignancy of structures derived from the embryonic neural crest. The hallmarks of its enigmatic character include its propensity for spontaneous regression under certain circumstances. Metastatic, High Risk (HR) NBL however is a serious disease at almost any age. Successful treatment requires intensive chemo/radio/surgery approach and biologic therapy using cis-retinoic acid and anti GD2 monoclonal antibodies. The Overall Survival (OS) and Event Free Survival (EFS) figures have improved in the recent years. Spontaneous regression or even cessation of tumor growth is not known in metastatic HR-NBL, and disease progression is inevitable if left untreated. Here we report a child who was initially diagnosed with HR metastatic NBL at the age of 10 months. The tumor involved his suprarenal gland, Bone Marrow (BM), pelvis and skull causing large tumor masses. He initially received 4 cycles of Chemotherapy (CTR) and then stopped for toxicity. He only had minimal response to CTR. However, he remained well thereafter for several years, well-adjusted with his tumors which were growing in parallel to his general growth. He presented to our hospital at the age of six years aiming to improve his appearance. In fact, he was not bothered by the disease and continued to lead normal life. His main problem came after entering primary school where he was continuously teased and bullied by his colleagues. Re-investigations confirmed active metastatic NBL. We believe that some undiscovered feature s of his tumor biology may have played a role in that unusual tumor behavior. We aimed at improving his facial appearance with cosmetic surgery. We initially treated him with CTR but he showed no response. His disease suddenly flared up a year later and rapidly progressed. Unfortunately, he died within few weeks as a result of disease progression. In this case report we discuss the cytogenetic and the molecular genetics features of NBL that could be behind the unique presentation and clinical course.

Keywords: Chemotherapy; Dinutuximab; High-risk; *MYCN* gene; Neuroblastoma; Spontaneous regression

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Introduction

NBL is a malignant disease of the sympathetic ganglia and adrenal medulla, structures derived from the embryonic neural crest. NBL is a rare childhood cancer. Over one third of NBL's are diagnosed in infants, and 90% are diagnosed before 5 years of age. The hallmarks of its enigmatic character include its propensity for spontaneous regression under certain circumstances especially limited stage tumors in very young children [1,2]. As a complex disease, many factors, such as age and stage of disease at diagnosis, and the molecular, cellular, and genetic features of the tumor determine whether it will spontaneously regress or metastasize and become refractory to therapy [2]. Amplification of the *MYCN* gene is found in 25% of cases and correlates with poor prognosis [3]. HR metastatic NBL is a serious disease at almost any age and if left untreated it results in progressive deterioration and ultimately inevitable death [4]. Successful treatment requires intensive neo-adjuvant CTR, surgical resection, consolidation with single or double tandem autologous BMT, Radiotherapy (RT), differentiation biologic therapy using cis-retinoic acid and immunotherapy using anti GD2 monoclonal antibodies (dinutuximab) [5,6]. The OS and EFS figures have improved in the recent years especially with the introduction of tandem ABMT and dinutuximab to reach near 55% and 50% respectively [7]. Here we report a young child who presented to our hospital at

the age of nearly six years after he was initially diagnosed with HR metastatic NBL at the age of 10 months. He only received 4 cycles of OJEC (vincristine, cisplatin, etoposide, and cyclophosphamide) CTR with minimal response. Parents decided not to continue treatment because of the severe complications. Surprisingly, he remained well for several years thereafter living along well with his tumors until he was brought to our hospital for problems concerning bullying at school because of his strange facial and body appearance. Re-investigations including true cut open biopsy confirmed active HR metastatic NBL. We believe that some undiscovered features of his tumor biology may have played a role in that unusual tumor presentation. In this case report we discuss the cytogenetic and the molecular genetics features of NBL that could be behind the unique presentation and clinical course.

Case Presentation

Our patient was perfectly well until the age of 8 month where he was diagnosed to have adrenal gland NBL with metastasis to the lungs, bones and BM. He was treated in his home country using the OJEC (vincristine, cisplatin, etoposide cyclophosphamide) CTR combination. He developed severe infective complication following the 3rd and 4th cycles of CTR and required intensive care admission for few weeks. Evaluation Computerized Tomography (CT) scan following the second and fourth cycles of CTR showed mild reduction in the size of his tumors Because of the severe toxicity and poor response, parents decided to stop CTR at that stage. To everybody's surprise, the child stayed well and kept growing and developing normally. His tumors kept growing up slowly in a more or less parallel rate to his general growth. Despite his obviously small mouth opening, oral cavity and severely distorted and overcrowded teeth his speech was reasonably clear and easily understandable. His school performance was amazingly good. However, and after he grew older and moved to primary school, children started to note his unusual appearance and started teasing and bullying him. At times, school they throw out comments in his face such as; you are scary? These comments made him to become very sensitive, easily emotional and he gradually isolated himself. Finally, and to avoid their teasing and sarcasms, he refused to go to school altogether. It was only by mere chance and while with the family in a shopping place, the father was approached by a notable community lady who facilitated his access to our hospital for treatment.

When arrived to our hospital, he was nearly six years old. He appeared generally well, energetic and interactive. Despite his strange external appearance, (Figures 1a-1c), he was a sweet child and was communicating in an appropriate despite slightly muffled language. His growth parameters and vital signs were normal for his age. A large tumor mass was seen occupying his right side of the skull and mandible. The skin overlying the tumor was full of dilated small veins. His right eye appeared slightly smaller than the left and was more or less almond shaped but both eyes were otherwise normal. The movement of his lower jaw was relatively restricted and asymmetric due to the presence of the tumor mass and hence his ability to open his mouth wide. His teeth as a result, were very distorted, overcrowded, misaligned and mostly decayed. The abdomen was clearly protruding forward. An easily palpable large, hard, non-tender soft tissue mass was felt occupying the whole right side and central parts of the abdomen. Other system examination was normal.

The general blood tests obtained at presentation to our hospital were all normal. The urine catecholamines were greatly elevated.

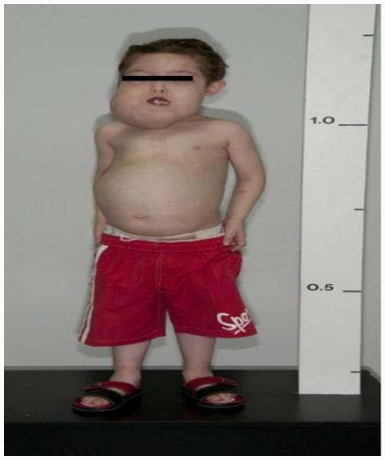

Figure 1a: The patient on arrival to our hospital. Note the average body built the normal height for age and the protruding abdomen.

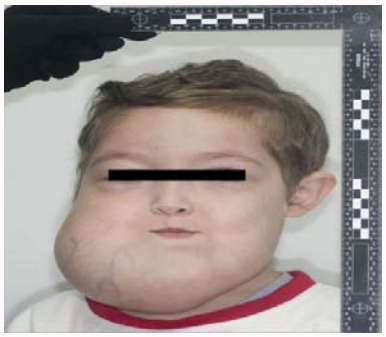

Figure 1b: The large tumor mass occupying the lower mandible and the right side of the face causing obvious facial asymmetry and a small looking mouth opening. Multiple very obvious connected networks of dilated superficial veins overlying the tumor over the right side of the face, the lower mandible and submandibular area.

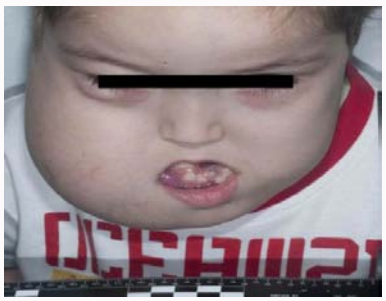

Figure 1c: The front teeth are distorted decayed and grossly misaligned.

CT scan examination showed large right suprarenal/retroperitoneal and pelvic soft tissue masses with calcifications, an anterolateral soft tissue mass attached to the right chest wall originating from a rib, a thoracic paraspinal soft tissue mass with intraspinal extradural extension but no spinal cord compression, a right mandibular mass extending intracranially into the anterior cranial fossa and the roof of the oral cavity. Multiple skull, rib and vertebral destructive infiltrative aggressive metastatic lesions (Figures 2a-2c). Meta-Iodo-Benzyl Guanidine (MIBG) scan showed intense pathological uptake in the right abdomen, pelvis, ribs, skull and multiple other skeletal sites (Figure 3). Nuclear technetium bone scan showed widespread bone metastasis (Figure 4). An abdominal mass biopsy was performed and

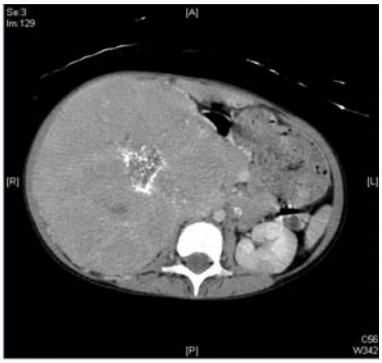

Figure 2a: CT scan of the abdomen showing the huge (14 cm × 12 cm) right upper quadrant heterogenous right side abdominal tumor crossing the midline with areas of necrosis extensive calcifications. The liver, spleen and pancreas are unremarkable.

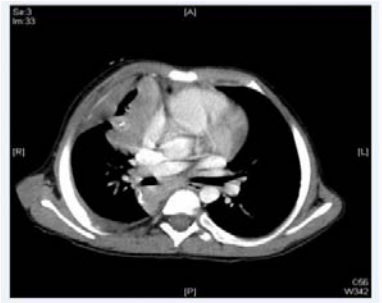

Figure 2b: The chest CT scan shows the large anterior mediastinal soft tissue mass (8 cm × 3 cm) with flicks of calcifications. Several smaller rib and pleural based soft tissue masses are seen in the anterior chest wall in addition to the para-cardiac area.

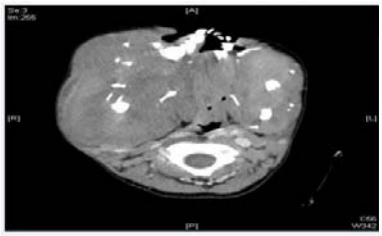

Figure 2c: CT of the head showing destructive deforming lesion involving both mandibles with huge soft tissue component more in the right side and extending into the base of the skull, and involve the sphenoid and zygomatic bones ant the maxillary air sinus in the left side.

histopathology confirmed undifferentiated, Shimada poor, HR-NBL. Bone marrow aspiration and biopsy showed extensive infiltration with NBL cells. BM aspiration and biopsy showed heavy infiltration with NBL cells.

Although the child did not appear to require urgent therapy, we started investigating his disease mainly to assess his exact clinical status before deciding the next move in his management. Because of the strange case scenario, we discussed the case in our Departmental Tumor Board meetings in the presence of the pediatric, ENT, plastic and maxillofacial surgery teams. We had also further discussed the case in the international NBL Network Web Based Tumor Board meeting and obtained opinions from international experts in the management of HR-NBL.

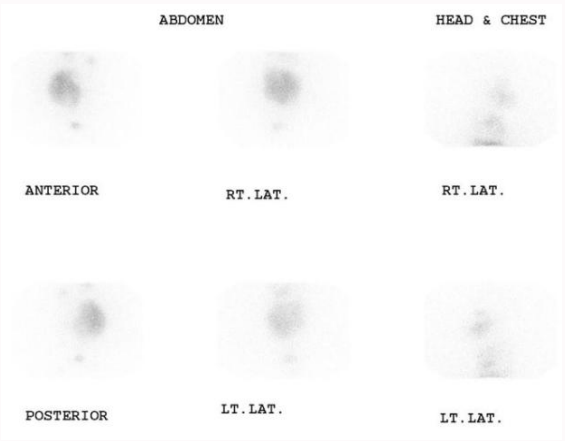

Figure 3: Base line nuclear I-131 MIBG scan showing the increased MIBG uptake in the area of the central abdominal tumor and metastatic disease at the right mandible, neck, mediastinum in addition to the proximal parts of both femurs.

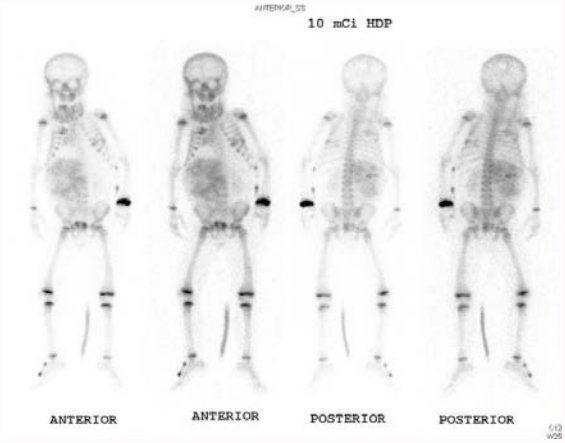

Figure 4: Base line Tc99m nuclear scan showing the huge abnormal uptake in the mid abdomen and metastatic disease involving the right mandible, maxilla, mediastinum and multiple rib bones.

The child has persistent, active, metastatic, HR-NBL at the age six years. The *MYCN* gene on the biopsy specimen was not amplified. At first presentation and from the first look, this sort of disease in fact requires intensive multimodality treatment approach and the chances for the treatment to succeed are modest. However, the big concern of the child and the family was his facial and abdominal appearance and what it brings to him in terms of teasing and sarcastic comments which in fact, had negatively influenced the whole family. In our opinion, that was probably the only reason that encourages us to go ahead and pursue ways to help this lovely child and his poor family. In addition, we took into account the severe nature of his active disease and the possibility of future flare up with the resultant devastating consequences on his health if left untreated.

After thorough discussion with the parents, we decided to start the treatment. Our primary aim was to improve his facial appearance, if that would be possible. But the big hurdle was to achieve the desirable result meanwhile he harbors an active malignant tumor. Our maxillofacial and plastic surgery colleagues were reluctant to do any cosmetic procedure in such a situation. Cutting through the active tumor to reconstruct his mandible and oral cavity could lead

to total collapse of the roof of his oral cavity. Our pediatric surgery colleagues had the same opinion with regard to the resection of the abdominal tumor. Both teams agreed that in order to do any fruitful cosmetic surgery for this boy, we should effectively treat the active tumor. During discussions in the International Global NBL Network Tumor Board meeting, all members agreed that we need to try and improve his general appearance but before that we should give treatment to cure his active disease. As per the panel suggestion we are giving him 6 cycles of cyclophosphamide 250 mg/M^2/day × 5 days and topotecan 0.75 mg/M^2/day × 5 days. He tolerated CTR and remained very however he CT and MIBG scans showed only minimal response, if any. We then started him on standard HR NBL induction CTR and gave him a total of 4 alternative cycles of cyclophosphamide 2.1 grams/M^2/day × 2 days, doxorubicin 25 mg/M^2/day × 3 days and vincristine 0.67 mg/M^2/day × 3 days (CDV) alternating with cisplatin 50 mg/M^2/day × 4 days and etoposide 200 mg/M^2/day × 3 days (CiE). He again tolerated CTR well but showed minimal radiological response (Figures 5a-5d). The BM remained heavily infiltrated with the disease. Shortly after receiving 4 cycles of standard CTR, both his facial and abdominal tumors were noted to reactivate and progressively increase in size. The child became progressively sick with huge abdominal distension and respiratory distress. The right mandibular tumor increased in size and protruded to fill out the oral cavity. At that stage, we planned to give him high dose MIBG therapy but he became very sick to tolerate. A palliative dose of RT was given to the right mandible and abdomen but no positive effect was observed. Unfortunately, it was only few days later when he lost his battle with the illness and died due to progressive disease.

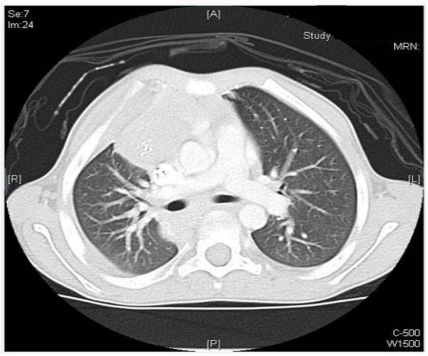

Figure 5a: Follow up CT.

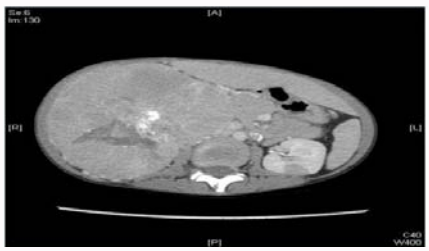

Figure 5b: Follow up CT.

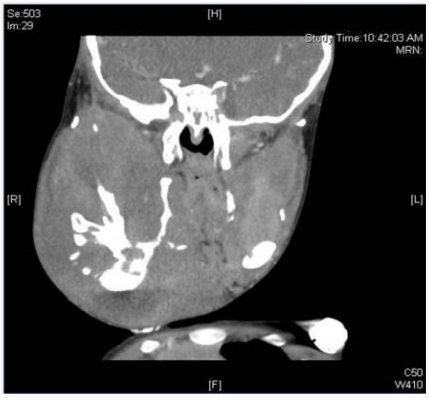

Figure 5c: Follow up CT.

Discussion

Our patient was diagnosed with HR metastatic NBL at the age of 10 months. He received 4 cycles of multi-agent CTR with minimal response. As a result, his disease had clinically stopped or very much slowed in progression. It is not clear why he suffered rapid disease reactivation and progression several years later when we intervened while trying to improve his general appearance. Unfortunately, he lost his battle with the disease and passed away nearly 12 months after his arrival to our hospital. To us, his disease clinical behavior with quiescent course then rapid reactivation several years later seemed to be very unusual. When HR-NBL is incompletely treated, such patients would soon develop disease progression and become very sick [8]. We asked world experts in some oncology centers around the world about their experience and they denied coming across a similar presentation (Baker DL, Perth, Australia, Matthay KK, San Francisco, USA, personal communication, April 2011). Our patient however and after the initial treatment, remained well with his disease for nearly four years without receiving further therapy. He attained normal growth and development for any normal child at his age. As it appeared to us, his disease reactivation and progression after a long period of being quiescent had in fact coincided with our interference with an open biopsy to confirm diagnosis and the subsequent CTR administration.

This unique disease presentation was further discussed in the St. Jude Hospital Children's Research, Memphis, TN, USA, and Global NBL network on-line tumor board. In principal, the panel agreed to try CTR before attempting reconstructive surgery. The parents were happy with the decision. In fact, and because of the unusual presentation and behavior of this patient's disease and the rich discussion it brought, some participants advised to prepare and publish this case for a wider benefit to the pediatric oncology community, no matter what ultimately happens to the patient's disease. We treated him with 6 cycles of cyclophosphamide and topotecan then 4 cycles of standard chemotherapy for HR-NBL but he did not show any response despite having frank histologically confirmed NBL.

As a heterogeneous disease, many factors (such as the age, stage of disease at diagnosis and the molecular, cellular, and genetic features of the tumor) determine whether NBL will spontaneously regress or metastasize to become refractory to therapy [2].

Progression of localized tumors such as NBL is closely associated to their local growth potential rather than to their metastatic spread [8]. NBL is thought to result from failure of neural crest cells differentiate, so understanding normal neural crest differentiation may help understand the tumor behavior better and identify novel targets for cure and, potentially, prevention of NBL [9].

Growth cessation and spontaneous regression are known

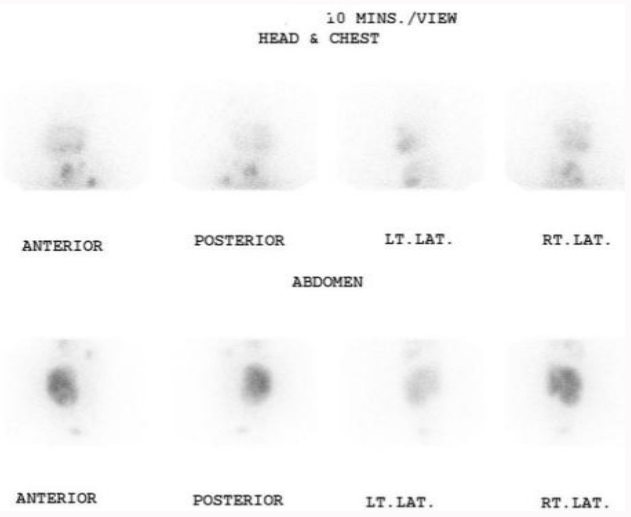

Figure 5d: MIBG scans showing almost the same tumor distribution, size and MIBG activity of the original NBL lesions.

phenomena in low and less frequently in intermediate risk NBL but are not observed in patients with HR-NBL [4]. However, and after wide literature review, we did not find a single reported case of growth cessation or spontaneous tumor regression in HR neuroblastoma.

Even after extensive literature review and discussions, we unfortunately were not able to identify a clear cause for this patient's disease behavior. Some of the known biological features of NBL however, may help explaining the events that took place following the arrival of the child in our hospital. Many of the international experts we consulted thought that the tumor behavior is most probably related to some unique cytogenetic and/or molecular features that were not recognized at the time of diagnosis and suggested sending the tumor specimen to specialized laboratories overseas to perform wider biologic studies.

The exact mechanisms responsible for spontaneous regression (and differentiation) of NBL are uncertain, but several mechanisms have been proposed to explain this phenomenon. Recent genomic and biological studies have shown dramatic heterogeneity in the clinical behavior of this disease, which spans from spontaneous regression or differentiation in some patients, to aggressive disease progression in others, despite intensive multimodality therapy. Evidence suggests several mechanisms to explain the phenomena including neurotrophin deprivation, humoral or cellular immunity, loss of telomerase activity and alterations in epigenetic regulation. Currently, the most druggable mechanism is the delayed activation of developmentally programmed cell death (apoptosis) regulated by the Tropomyosin receptor kinase (Trk) A pathway [4,10].

Understanding the molecular program of NBL at diagnosis may provide tools for improving risk stratification and deciding the correct therapy. The availability of NBL genomic profiles improves the prognostic ability. Several groups have developed gene expression-based approaches to stratify NBL patients and described prognostic gene signatures [8,11,12].

Based on cytogenetic profiles, NBL can be divided into three major subtypes-subtype 1, 2A and 2B. Subtype 1 is characterized by numerical chromosome alterations resulting in hyperdiploidy or near triploidy, but with few if any Segmental Chromosomal Abnormalities (SCA's). High expression levels of the Trk A are common to almost all subtype 1 tumors. Patients with these tumors have favorable features (such as young age and low tumor stage) and outcomes. Subtype 2 is characterized by near diploidy and recurrent SCA's. Many of these tumors have an unbalanced gain of the chromosome 17q, and most over express both Trk B and its ligand. This last subtype can be further divided into subtype 2A, which frequently has segmental loss of chromosomes 3p, 4p, and/or 11q; and subtype 2B, which has deletion of chromosome 1p and/or *MYCN* amplification. NBL's of subtypes 2A and 2B are associated with older patient age, advanced tumor stage and a worse clinical outcome, with subtype 2B tumors being the most aggressive [4,13].

The myelocytomatosis viral related oncogene NBL derived (*MYCN*) amplification (encoding a transcription factor), a strong predictor for survival, discovered in the 1980's, and occur in about 40% of patients with advanced stage NBL. *MYCN* (2p 24.3) amplification (>10 copies) is associated with poor survival in NBL, even in patients with localized disease and those aged less than 18 months at diagnosis. *MYCN* amplification mainly works by blocking retinoic acid cell differentiation [10,13].

SCA's are frequent in NBL and are associated with worse outcome. About 1% to 2% of patients with NBL have a family history of this disease. Two germ line gene mutations; *ALK* and *PHOX2B*, were recently discovered and were found in nearly 80% of hereditary NBL [3,4,7].

HR-NBL, in particular the therapy-resistant subset with chromosome 11q-deletion, was found to be inflammatory driven. This group of NBL's is characterized by high expression of the COX/microsomal prostaglandin E synthase-1 (mPGES-1)/Prostaglandin E2 (PGE2) pathway that correlates with metastatic stage and poor clinical outcome. The infiltrating cancer-associated fibroblasts were shown to be expressing mPGES-1, the essential enzyme for synthesis of PGE2, promoting tumor growth, angiogenesis, and metastatic spread. Treatment targeting this inflammatory pathway may provide therapeutic option for HR-NBL and other cancers in the future [14].

Deep Whole Exome Sequencing (WES) studies or Whole-Genome Sequencing (WGS) analysis of NBL tissues have identified relatively few additional gene mutations that were not otherwise known to have a role in this disease. In addition to *MYCN* amplification, Manuscript Activating Mutations (MAM's) or rearrangements of ALK gene were found in 8% to 10% of sporadic tumors. Furthermore, mutations in *ATRX*, *ARID1A*, *ARID1B*, *MYCN*, *PTPN11* and *NRAS* were found in 1% to 3% of cases. Oncogenic activation of *FOXR1* by 11q23 intrachromosomal deletion-fusions has been identified in only a few NBL cases [4,15].

Genome-wide searches are uncovering striking differences in the prevalence of mutations among tumor types, from very frequent among adult tumors such as melanomas to rare among pediatric cancers such as NBL. In melanoma, the rich epitope landscape, or mutanome, has been successfully exploited for T-cell based immunotherapy [4,16]. But in NBL with a small mutanome, the classic immunotherapy model may be difficult to apply. Antibody-based instead of common T-cell-based therapy directed at fetal oncologic differentiation antigens has provided a viable alternative. The current immunotherapy strategy uses anti-GD2 monoclonal antibodies to direct the traffic of FcR-bearing NK cells and granulocytes, stimulating them through the FcR CD16 and CD32, respectively is proving successful [2,17,18].

As we stated before, our patient's tumor showed signs of activity at presentation but for an unknown reason the tumor was not obviously growing and remained dormant for several years. We aimed at reducing his tumor size and clear metastasis but he showed no response. It is not clear whether our manipulation of this tumor with biopsy and CTR as we thought resulted on re-ignition of this tumor growth and caused it to rapidly regrow again and ultimately resulted on the child's demise. In retrospect, we wonder whether leaving the child alone with no active interference was in fact the better choice for his case.

The initial cytogenetic studies of our patient, conducted in our hospital showed no specific abnormalities. The *MYCN* gene was not amplified. Unfortunately, we were not able to send for more advanced genetic and molecular studies because of patient eligibility issues. Further molecular studies of the tissue specimen might have helped in explaining the activation and rapid progression of the tumor following re-biopsy. However the initial halt in growth following therapy at first presentation remain to be explained.

Acknowledgment

The authors would like to thank Dr. Aeishah Alazmi for her kind technical help in preparing the illustrations for publication.

Ethical Considerations

Written consent for publication has been obtained from the patient's father.

This case report was reviewed and approved by the hospital research office and the Institutional Review Board (IRB). Approval letter #IRBC/1704/19.

Authors Contribution

Adil Abdelhamed Abbas: Full manuscript preparation and final formatting.

Khalid Abdalla Khalid: Participated in manuscript preparation and final review.

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