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Massive Intra-Tumor Hemorrhage during Induction Chemotherapy in Neuroblastoma: A Case Series Report

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Abstract

We describe 5 children with high risk neuroblastoma (NB) who, during the induction phase of therapy, were admitted with circulatory shock because of massive intra-tumor bleeding. Patient's intensive supportive care with fluid resuscitation, blood and blood product's transfusion succeeded to restore hemodynamic stability. Surgical intervention to control bleeding was necessary in two of the children. All children survived the massive hemorrhage to continue their treatment as per protocol. Overall prognosis was not affected by this incident.

Abbreviationsm

NB:Neuroblastoma; CT: Computed Tomography; IRB: Institute Review Board; HR: High Risk

Introduction

NB is the most common extra-cranial solid tumor in children. Multiple risk factors have been identified and subsequently used in treatment protocols with the aim of increasing survival and decreasing treatment related morbidity. Treatment of NB is multi-disciplinary and active measures are used to ensure un-interrupted therapy. At presentation and before initiation of chemotherapy CT scan in some children shows intra-tumor single or multiple foci of hemorrhage [1]. On rare occasions young infants with NB present with acute massive hemorrhage that result from spontaneous tumor rupture or follows minimal trauma [2,3]. Acute massive hemorrhage without tumor rupture however, is an exceptional event. Over the preceding 10 years we encountered few cases of NB who presented with massive hemorrhage shortly after initiation of their chemotherapy protocol and their tumor on CT scan remained intact. The aim of our report is to bring into attention this peculiar, potentially lethal incident and to share our experience in its diagnosis and treatment.

Case Report

With IRB approval, we retrospectively reviewed charts of all NB patients at King Hussein Cancer Center (KHCC) between 2006 and 2015, and found 5 children who developed acute hemorrhagic shock prior to local surgical control. Children are treated according to our institutional protocol which incorporates 6 cycles of multi-agent chemotherapy followed by surgery, high dose chemotherapy with stem cell rescue, radiotherapy, and cis-retinoic acid orally. Massive hemorrhage was defined as image-proven, intra-tumor bleeding that lead to hypotension.

Results

All 5 children were initially assigned to the high-risk group (Table 1). The primary tumor had been biopsied in 4 patients. The onset of hemorrhage was 7-10 days following cycle 1 of induction in all patients except in one patient (patient 3), where hemorrhage followed cycle 5 (Table 2). All patients had significant drop in their Hemoglobin (>2 gm/dl) and platelets. Their coagulation profiles were normal throughout the course of admission. All required massive blood and blood product's transfusion to restore hemodynamic parameters, replace blood loss, and maintain a stable hemoglobin level. In one patient (patient 1), chemotherapy doses were subsequently temporarily reduced for one cycle before resuming full dose.

Table 1: Demography, tumor biology, pathology, risk group, outcome.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	12 m	21 m	54 m	28 m	132 m
Primary	L adrenal	L adrenal	L adrenal	R adrenal	L thoracoabdominal
INPC	Poorly D	Poorly D	Not done	Poorly D	Poorly D
MYCN	Amp	Amp	Not Amp	Lost	Amp
Bone marrow	Negative	Negative	Positive	Negative	Positive
Bone	Positive	Negative	Positive	Negative	Negative
Risk group	HR	HR	HR	HR	HR
Pathology at GTR	GNB	Mature neural cells	None	GNB	Total necrosis
Overall Outcome	Relapse Died 21 m post diagnosis	Remission Alive 4 years	Progression Died 18 m post diagnosis	Relapse Died 14 m post diagnosis	Remission Alive 4 years

L: Left; R: Right; D: Differentiated; Amp: Amplified; HR: High Risk; Poor D: Poorly Differentiated; GNB: Ganglioneuroblastoma; GTR: Gross Total Resection.

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Table 2: Episodes of Hemorrhage, management and outcome.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Onset/ cycle	1st cycle	1st cycle	5th cycle	1st cycle	1st cycle
Treatment	Conservative	Conservative	Conservative	Conservative	Conservative
Episode 1	Stopped	Stopped	Stopped	Stopped	
Episode 2		Yes			
Surgery		Yes			Yes
Outcome	Survived	Survived	Survived	Survived	Survived

All patients had abdominal pain, increased distention, severe pallor, and hypotension. CT scans with IV contrast showed increase in tumor size with presence of blood within the tumor and none in the peritoneum (Figure 1). Angiography was attempted in the first two cases and as it did not show any major blood vessel leak, it was not attempted in the remaining children.

In patient 5, who had a thoraco-abdominal tumor, hemorrhage occurred in both compartments. Hemorrhage into the thorax however, remained active, which mandated operative control.

In patient 2, a second episode of massive hemorrhage occurred during the same admission and despite massive transfusion of blood and crystalloids, hemorrhage persisted and the child remained hemodynamically unstable. The multidisciplinary team decision supported operative control of the hemorrhage.

All children survived massive hemorrhage. In the 2 children where surgical control was required (patient 2 and patient 5), the tumor contained viable poorly differentiated tumor cells. Assessment after cycle 5 showed tumor response by volume with partial remission (N=4) or complete remission (N=1). Histopathology of the respected tumor at the time of local control in the 4 patients with residual masses showed differentiated tumor cells in 3 and complete necrosis in another one. Similar to children with high-risk neuroblastoma treated by the same protocol, 2 patients only were long-term survivors while the other 3 relapsed and died later (Table 1).

Discussion

Approximately half of NB children at presentation have disseminated disease and are assigned for high-risk treatment [4]. Clinically silent hemorrhagic foci inside the primary have been described mainly in adrenal NB and at different ages 1, 5 at initial presentation [5]. Such foci are frequently seen on repeat imaging at the time of local control. Hemorrhage has been reported in newborns mainly with adrenal cystic NB, unilateral and bilateral where it remains contained within the capsule and is not massive to cause hypotension [6-9]. Such children are primarily managed surgically with excellent long term prognosis as the majority has favorable Shimada histology [10]. Massive hemorrhage and circulatory shock has been repeatedly ascribed to tumor rupture in newborns. The first report was in 1982 and rupture has been labeled spontaneous rather than related to birth trauma [11]. Massive hemorrhage has been reported during infancy where some presented following minor trauma 3 and tumor rupture was typically identified during laparotomy [2,12]. Immune-induced tumor ischemia was cited as a cause for rupture in an infant with thoracic NB [13]. Outside this spectrum, massive hemorrhage

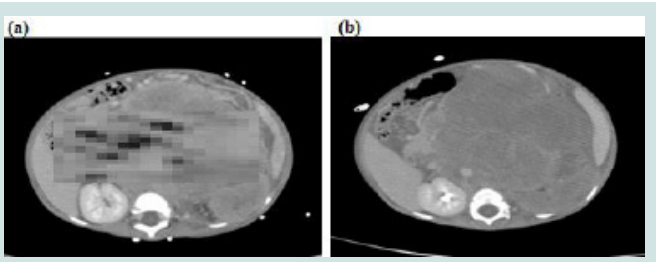

Figure 1: (a) Abdominal CT scan shows Left adrenal tumor at the time of diagnosis and (b) at the time of the event.

inside an intact tumor causing circulatory shock is an unexpected and previously unreported event. In our patients, it occurred during the induction phase of treatment. The presenting features were similar to those with tumor rupture.

Bleeding can be triggered by necrosis in a rapidly proliferating NB containing mainly un-differentiated or poorly differentiated cells. It occurs when the integrity of the endothelium is disrupted and the coagulative process is switched off. In massive hemorrhage it is thought that in response to chemotherapy, a large central area of viable and well-vascularized tumor cells dies [3]. Infarction of fragile small feeding vessels inside the center of the tumor can be an additional cause of massive bleeding. At the periphery, the tumor capsule remains intact, leading to large but contained blood loss. We did not identify a single major blood vessel leak on angiography in the first 2 cases. Although all children had low platelets count, an effect of chemotherapy, none had abnormal coagulation profile.

Intensive non-operative management was sufficient for the hemorrhage to stop in 4 of the 5 children. Surgical intervention was required on 2 occasions; in one child (patient 5), to control the initial continuing hemorrhage and in another child (patient 2) to control a second episode of massive bleeding. As complete tumor resection was not feasible the aim of the operation was to control hemorrhage through safe incomplete resection. A CT scan was used to map the zone of hemorrhage. Gross total resection of the remaining tumor was achieved at a second surgical session at the time of local control. There has been no hemorrhage-related mortality. Overall survival of this small group of children on high-risk protocol remains lower than in children with spontaneous tumor rupture [2]. Long term survival was possible when either total tumor necrosis or complete maturation was seen. Massive hemorrhage during induction chemotherapy might have been encountered but was not reported by collaborative groups. It remains a possibility that we receive patients with big size undifferentiated or poorly differentiated tumor cells that are more likely to bleed when treated with chemotherapy.

Conclusion

This report remains a retrospective analysis of a small number of children. Nevertheless, massive hemorrhage inside NB tumor can occur during initiation of chemotherapy. Intensive resuscitation and expectant management pending spontaneous arrest of hemorrhage has been sufficient in the majority of instances. Surgical intervention however, remains an option in continuing hemorrhage. The zero mortality rates related to this incident, one can safely conclude that it has no effect on the overall survival.

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