Thromboelastometry-guided surgery in neuroblastoma complicated with disseminated intravascular coagulation

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ABSTRACT

Background. Disseminated intravascular coagulation (DIC) is a rare oncological emergency. We report a pediatric neuroblastoma complicated with DIC which required thromboelastometry-guided surgery.

Observation. A 6-year-old female diagnosed with intermediate risk adrenal neuroblastoma developed tumor-related DIC after chemotherapy first cycle. She remained stable without clinical bleeding and emergent tumor resection guided by intraoperative-thromboelastometry was decided. DIC resolved early after surgery and complete remission was achieved.

Conclusion. Treatment of the underlying condition is critical to manage DIC. Thromboelastometry can guide goal-directed therapy, including surgery in pediatric patients. However, larger studies are needed to examine its applicability in different clinical settings, such as cancer related DIC.

KEY WORDS: Disseminated intravascular coagulation; Neuroblastoma; Cancer; Rotational thromboelastometry; Children.

CIRUGÍA GUIADA POR TROMBOELASTOMETRÍA EN NEUROBLASTOMA COMPLICADO CON COAGULACIÓN INTRAVASCULAR DISEMINADA

RESUMEN

Introducción. La coagulación intravascular diseminada (CID) es una urgencia oncológica poco común. Describimos el caso de un neuroblastoma pediátrico complicado con CID que precisó de cirugía guiada por tromboelastometría.

Caso clínico. Paciente de seis años diagnosticada de neuroblastoma suprarrenal de riesgo intermedio que desarrolló CID asociada al tumor tras el primer ciclo de quimioterapia. Permaneció estable sin hemorragia clínica, decidiéndose una resección tumoral de urgencia guiada por tromboelastometría intraoperatoria. La CID se resolvió poco después de la cirugía, consiguiéndose una remisión total.

Conclusión. El tratamiento de la patología subyacente es clave a la hora de manejar la CID. La tromboelastometría puede guiar la terapia orientada a objetivos, también en cirugías realizadas en pacientes pediátricos. No obstante, hacen falta mayores estudios que analicen su aplicabilidad en distintos contextos clínicos, como la CID relacionada con cáncer.

PALABRAS CLAVE: Coagulación intravascular diseminada; Neuroblastoma; Cáncer; Tromboelastometría rotacional; Niños.

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a systemic process with the potential for causing thrombosis and hemorrhage[(1)]. It is a well-recognized entity both in malignant and non-malignant conditions, with sepsis being the most common cause in children[(2)]. In pediatric malignancies, it is more frequently described in acute leukemia although it has been described in solid tumors (ST), such as neuroblastoma[(3-7)].

Early identification of the underlying disorder responsible for DIC is critical to improve survival[(3,4,8,9)]. Management of tumor related-DIC may require surgical resection of the primary tumor with an increased risk of uncontrollable bleeding given the ongoing DIC.

In the past few years, viscoelastic testing (VT), such as rotational thromboelastometry (ROTEM) and thromboelastography (TEG), have gained a renewed interest in monitoring and guiding goal-directed therapy of specific coagulation alterations in adult and pediatric patients[(10-13)]. ROTEM is an enhanced modification of TEG, although there has been no evidence suggesting clinical superiority of one system over another. Both are methods of hemostatic analysis that provide a real-time, holistic view of ex vivo clotting. This allows rapid diagnosis of specific

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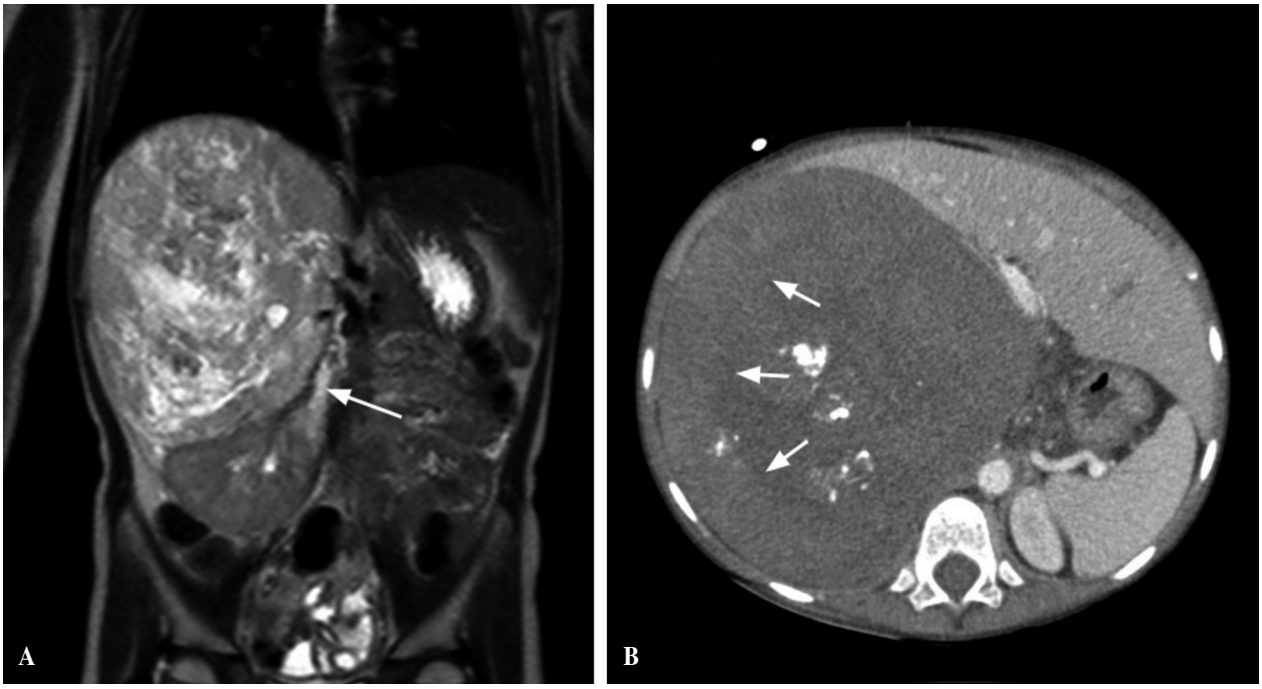

Figure 1. A) Coronal T2- enhanced abdominal MRI at diagnosis. An heterogeneous well defined large right adrenal lesion is seen, with necro-cystic areas and calcifications. There is a secondary mass-effect displacement of the liver and the ipsilateral kidney, which are pushed posteriorly and caudally, respectively. The lesion is in contact with the right renal vein, but no infiltration is seen (white arrow). B) Axial abdominal CT scan with contrast one month later. There is an increase in the size of the adrenal mass, maintaining the necro-cystic areas seen previously. A newly viewed shape-moon hyperdense image is seen on the lateral border of the mass (white arrow), which could be associated with internal bleeding.

coagulopathies, therefore suggesting specific treatments, which may reduce transfusion requirement and decrease hemorrhage and mortality[10-12].

We present a case of a pediatric patient with an adrenal neuroblastoma who developed DIC and required ROTEM-guided surgery.

CASE DESCRIPTION

A 6-year-old female presenting with a long-term gradually increasing abdominal mass and no constitutional syndrome was admitted to our hospital. On initial laboratory tests both serum levels of neuron-specific enolase and urine cathecolamines were raised. Abdominal MRI showed and large T1-hypointense and T2-hyperintense right adrenal mass with areas of necrotic degenerations and calcifications (Fig. 1A). After undergoing an ultrasound-guided core needle biopsy, a whole-body positron emission tomography-CT scan and bone marrow biopsy, a diagnosis of a localized differentiated neuroblastoma (schwannian stroma-poor) was obtained. No karyotype abnormality was observed and n-myc was not amplified.

According to LINES 2019 (Low and Intermediate risk Neuroblastoma European Study)[14], she started chemotherapy with carboplatin and etoposide. On day 18 post-chemotherapy she developed abdominal pain and vomiting. Physical examination showed abdominal distension and tenderness on the right upper quadrant.

Laboratory test showed hyperregenerative anemia, mild thrombocytopenia, hypofibrinogenemia, prolonged clotting times (protrombine time [PT] and active partial time of tromboplastine [APTT]) and increased D-dimer levels. No signs of acute bleeding, hemolysis or microangiopathy (specifically no schistocytes in the blood smear) were found. There was no evidence of organ dysfunction or sepsis. Thoracoabdominal Computed Tomography (CT) showed increased tumor size with doubtful signs of bleeding but no vascular thrombosis or metastasis (Fig. 1B).

Diagnosis of tumor-related DIC was stablished and supportive therapy with blood component transfusions and low molecular weight heparin prophylaxis was started. However, although she remained hemodynamically stable without clinical bleeding, DIC worsened, and an emergency tumor resection guided by ROTEM (ClotPro®) was scheduled. Supportive therapy was intensified, obtaining optimal preoperative lab results: PT 20 s, APTT 40 s, fibrinogen 0.9 g/L, platelets 75.000/µl, hemoglobin 17 g/dl. Preoperative ROTEM test values were as followed: EX test (tissue factor (TF)-activated assay) clotting times (CT) 90 s (reference values: 37-84 s), EX test maximum clot firmness (MCF) 59 mm (53-68 mm), IN test (ellagic

acid-activated assay)-CT 120 s (96-224 s), IN test-MCF 58 mm (48-66 mm). Only FIB test (TF-activated assay using cytochalasin D and glycoprotein IIb/IIIa inhibitor for platelet inhibition)-MCF was diminished to 5 mm (12-38 mm), which was compatible with hypofibrinogenemia and/or fibrin polymerization defect. No sign of hyperfibrinolysis was found. At that time, additional platelet transfusion and fibrinogen concentrate were administered.

Intraoperative-ROTEM was used to guide hemostatic management, without evidence of coagulopathic bleeding, and normal ROTEM values at the end of the surgery were observed: EX test-CT 80 s, EX test-MCF 60 mm, FIB test 15 mm, IN test-CT 129 s, IN test-MCF 51 mm. On postoperative day 1, she developed anemization with haemodynamic instability due to acute bleeding within the surgical site. However, no invasive interventions were needed and DIC resolved early after surgery, allowing to discharge the patient on the post-operative day 11 with no other major complications.

Pathology of the specimen showed great areas of necrosis and hemorrhage with signs of capsular rupture. She remains in complete remission 12 months after surgery. There was consent from both parents and patient for publication of the case.

DISCUSSION

DIC is a well-known complication of ST and hematological malignancies. In pediatric cancer, although uncommon, it has been described in almost all histologic types of ST[3-6].

Krishnan et al evaluated 73 cases of DIC in pediatric ST and found a higher propensity for DIC in patients <1 year with an advanced disease[4], although it has been described in older patients with localized disease as shown in our case.

Several tumor-cells properties have been described to be associated with cancer-related DIC. Tumor cells can either produce pro-coagulant molecules including tissue factor and a cancer procoagulant, or express fibrinolytic proteins such as annexin-II, urokinase-type plasminogen activator, tissue-type plasminogen activator and proteases. The final consequence is the uncontrolled production of thrombin[4,8,9].

Analyzing specifically our patient, these mechanisms may have contributed[4,8,9], however, partial tumor rupture (TR) may have also played a role. Both the pathology report and a new half-moon shape image within the tumor seen on the CT was consistent with capsular rupture, along with the presenting symptoms of sudden abdominal pain, abdominal distension, anemia, and coagulation disorder[15].

TR is an uncommon, life-threatening event in neuroblastoma. According to Qin et al., it occurs mostly in high-risk neuroblastoma and these patients are more prone to recurrence[15]. Primary tumor diameter >13.20 cm and n-myc gene amplification are independent risk factors for its occurrence. It can be either spontaneous or occur during or after the first cycle of chemotherapy, as seen in our patient. Probably, the large tumor size and its necro-cystic components, added to the vascular toxicity of chemotherapy[15,16] could ultimately led to TR and subsequently to DIC in our patient.

Regarding treatment, the therapeutic cornerstone of DIC is the adequate management of the underlying disorder. In fact, if the malignant disease can be brought in remission, DIC will generally resolve[3,4,8,9].

Surgical indications for neuroblastoma depend on the evaluation of imaging defined risk factors[17] and the patient clinical status. Although our patient was stable and the tumor was potentially resectable[14,15,17] given the high risk of fatal bleeding, an interventional tumor embolization was suggested but it was ultimately dismissed after a multidisciplinary analysis including oncologists, haematologists, interventional radiologists, surgeons and anesthesiologists.

ROTEM and TEG are increasingly being incorporated in vertical algorithms to diagnose and treat bleeding in cases at risk for hemorrhage including perioperative cardiac surgery patients, liver transplantation, trauma, and orthopedic surgery. Both systems have also been investigated in other areas, such as sepsis, obstetric hemorrhage, inherited bleeding disorders or perioperative thromboembolism[10-13].

Furthermore, VT has extended to some pediatric fields, including cardiovascular surgery, trauma and sepsis[18-20]. To our knowledge, this is the first case report on ROTEM-guided therapy in cancer-related DIC, which allowed a successful surgery.

Certainly, VT remains a relatively novel method of assessment of hemostatic competence, and no large trials have been conducted to date. Nonetheless, current evidence appears favorable in reducing blood components transfusion, especially in cardiac surgery patients, and it may reduce mortality[21]. Undoubtedly, future studies will further elucidate its impact on patient survival and examine its use in different clinical settings and age range.

In conclusion DIC is an uncommon but well-known complication of pediatric malignancies. Although challenging, treatment of the underlying condition is critical to reduce mortality. ROTEM reliably detects specific coagulation abnormalities, and can guide goal-directed therapy, including surgery in pediatric patients. Nonetheless, larger studies are needed to examine its applicability in different clinical settings, such as cancer related DIC.

CONFLICT OF INTERESTS

Authors declare they have not conflict of interest with the commercial suppliers of ClotPro®.

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