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Congenital infantile fibrosarcoma: Association with bleeding diathesis

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Patient: Male, 2 month
Final Diagnosis: Congenital infantile fibrosarcoma
Symptoms: Bleeding
Medication: Vincristine • actinomycin • cyclophosphamide
Clinical Procedure: Surgical resection
Specialty: Pediatric Oncology

Objective: Diagnostic/therapeutic accidents

Background: Congenital infantile fibrosarcoma (CIF) is a soft-tissue tumor occurring during the first 2 years of life, most commonly in the extremities. CIF is frequently initially misdiagnosed as a vascular tumor, but its association with bleeding and coagulopathy has not been well characterized.

Case Reports: We describe 2 infants with CIF presenting with bleeding and coagulopathy, requiring urgent intervention. Both patients did well; one underwent partial resection followed by chemotherapy, and the other received 2 cycles of chemotherapy followed by gross total resection. We also provide a review of all reported cases of coagulopathy in the setting of CIF in the English literature, uncovering an association that seems to be more prevalent in patients diagnosed in the neonatal period, with associated anemia and thrombocytopenia, and a significant mortality rate.

Conclusions: CIF needs to be considered in the differential diagnosis of vascular congenital tumors, especially when there is evidence of bleeding, anemia, or thrombocytopenia.

Key words: congenital infantile fibrosarcoma • bleeding • vascular tumor

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Background

Congenital infantile fibrosarcoma (CIF) is a soft-tissue sarcoma of infancy and young childhood, and is generally defined as fibrosarcoma occurring in children below 2 years of age. However, infantile fibrosarcoma may occur in children up to 5 years of age, and in such cases cytogenetic confirmation may be warranted. Histologically, CIF is similar to adult fibrosarcoma but the clinical course is significantly less aggressive [1,2]. A distinctive feature is the specific translocation t (12; 15) leading to the gene fusion *ETV6-NTRK3* [1,3]. The primary treatment is surgical resection, and chemotherapy is used in non-resectable tumors [1,2,4]. Consumptive coagulopathy is a rarely reported but life-threatening event in CIF. In this report, we describe 2 patients with CIF presenting with bleeding. We discuss the literature pertaining to bleeding and coagulopathy in CIF, and modalities of treatment.

Case Report

The first patient was a 2-month-old boy born at term, who presented with a mass over the dorsum of the right hand. The mass was noted to grow rapidly over a period of 1 week and then bled. Laboratory tests showed a hemoglobin level of 9.7 g/dl, hematocrit of 26%, and a platelet count of 29 000/cu.mm^3. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal, but fibrinogen level was low (<1 g/dL). The child received urgent platelet, packed red blood cell (PRBC), and fresh frozen plasma (FFP) transfusions, and an urgent resection of the mass was attempted. Subtotal resection revealed a 5.2×4.7×1.3 cm poorly circumscribed mass infiltrating the subcutaneous tissue. Microscopically, it was composed of sheets of solidly packed, spindle-shaped cells arranged in bundles and fascicles, imparting a herringbone appearance, with several mitotic figures per high-power field (Figure 1A). Immunohistochemical staining was positive for vimentin and negative for MyoD, Myogenin, Cytokeratin, Neuron-Specific Enolase, and CD99. Postoperative MRI showed 2 residual separate masses in the hand and forearm, extending between the metacarpal bones and infiltrating the inter-osseous palmar musculature, with heterogeneous signal intensity and enhancement after contrast administration (Figure 1B). Because complete excision was not feasible without functional compromise, chemotherapy was given using VAC regimen (Vincristine 0.05 mg/kg, Dactinomycin 0.025 mg/kg, and Cyclophosphamide 25 mg/kg, at 3-week intervals). After 4 cycles, clinical and imaging evaluation showed a decrease in tumor size, with a complete response after a total of 8 cycles (Figure 1C). No definitive local control was pursued. The patient remains tumor-free 3 years after end of treatment.

The second patient was a 2-month-old full-term boy born to first-degree consanguineous parents. He had a whitish mass, noted since birth, on the medial aspect of his left arm. A few days prior to presentation, the mass rapidly increased in size, with visible blood vessels that bled upon touch. At presentation the child was pale, hypoactive, and had profuse oozing of blood and purulent discharge from the mass. Laboratory evaluation showed hemoglobin of 6.3 g/dl, hematocrit of 19%, and platelet count of 313 000/cu.mm. PT, aPTT, and fibrinogen levels were normal, while D-dimers were slightly elevated at 207 ng/ml. The child received PRBC transfusion and antibiotics. CT scan revealed an 8.3×5×2.7 cm, highly vascularized mass over the medial aspect of the left arm, with areas of necrosis (Figure 1D). Biopsy showed infantile fibrosarcoma with several mitotic figures per high-power field, with similar immunostaining features to the first case above. Because of the large tumor size, neo-adjuvant chemotherapy was given (VAC every 3 weeks), to facilitate surgical resection. After the second

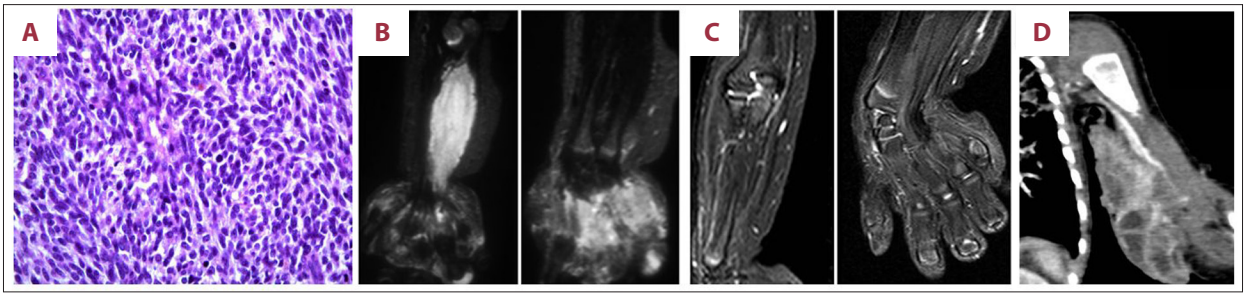

Figure 1. (**A**) Sheets of solidly packed, spindle-shaped cells arranged in bundles and fascicles, imparting a herringbone appearance, with several mitotic figures and vascular rich pattern. (**B**) MRI of the right forearm (right image) and right hand (left image); coronal STIR images showing a 6×2×1.5 cm high signal intensity mass involving the flexor digitorum profundus muscle and extending to the flexor digitorum superficialis muscle. Similar infiltrative mass is extending between the metacarpal bones and involving the interosseous muscles. Both the ventral and dorsal aspects of the hand were involved. (**C**) Follow-up MRI of the hand and forearm after end of therapy. Coronal STIR images showing normal signal intensity of the soft tissues with no evidence of recurrent or residual tumor. (**D**) CT scan of the left arm with IV contrast administration. Large heterogeneously enhancing soft tissue mass measuring 8×3 cm and showing areas of enhancement and necrosis.

Table 1. Summary of reported cases of CIF associated with bleeding diathesis at diagnosis.

Year [ref#]	N	Age	Site	Coagulopathy	Treatment	Outcome
1989 [5]	1	Prenatal	Arm	Bleeding	Resuscitation	Died at birth
1993 [6]	1	Prenatal	Chest wall	Hydropis fetalis, anemia, TCP, prolonged PT, PTT	None	Died at day 1 of life
1995 [7]	1	Prenatal	Thoracic	Hydropis fetalis	None	IUD
1995 [8]	2	Birth	#1: Scapula #2: Cervico-occipital region	#1: Anemia, TCP, low fibrinogen, high D-dimers #2: TCP, low fibrinogen, prolonged PTT, high D-dimers	S+CT S	NED at 2y NED at 1y
1997 [9]	1	At birth	Left thoracic mass	Hydropis fetalis Anemia, TCP	None	Died at day 3 of life
1999 [10]	1	Birth	Arm	Anemia, TCP	S*	NED at 6 y
1999 [11]	1	27 days	Forearm	Anemia	S	NED at 2.5y
2003 [12]	1	Birth	Hand	Anemia	CT	NED at 30 m
2004 [13]	1	Birth	Palm	Anemia, TCP, prolonged PT, PTT, low fibrinogen	S+CT	NED at 16m
2004 [14]	1	Prenatal	Neck	Hydropis fetalis	None	Died at birth
2006 [15]	1	Prenatal	Hand	Anemia, TCP, prolonged PT, PTT, low fibrinogen, high D-dimers	S+CT	NED at 33m
2006 [16]	3	Birth 4 weeks Birth	Palm Hand Hand	#1: TCP #2 and #3: Bleeding	S*+CT S* S*	NED at 2y NED at 2y NED at 8m
2008 [17]	1	Prenatal	Thoracic	Anemia	S	NED at 6 mo
2011 [18]	1	Prenatal	Leg	Hemorrhagic shock	S*	Died at 8 days
2012 [19]	1	Birth	Elbow	Bleeding	S+CT	NED at 4y
2012 [20]	1	Prenatal	Thigh	Anemia, TCP	S	NED at 2.5y
2012 [21]	1	Birth	Leg	Bleeding diathesis TCP	S*	NED at 2 y
2012 [22]	1	Birth	Foot	Anemia, TCP	S+CT	NED at 3 y

TCP – thrombocytopenia; PT – prothrombin time; PTT – activated partial thromboplastin time; S – surgery; CT – chemotherapy; NED – no evidence of disease; IUD – intrauterine demise; * – amputation.

cycle of chemotherapy, the patient developed life-threatening hepatopathy associated with coagulopathy, requiring FFP and cryoprecipitate. After supportive care and recovery, and because of the toxicity ascribed to chemotherapy, surgical resection of the tumor was pursued, with gross resection but microscopically positive margins. No further therapy was administered. Three years after follow-up, the patient is free of disease and sequelae.

Discussion

Approaches to treatment of CIF may vary from simple observation to surgical intervention, chemotherapy, or both. Surgically, subtotal resection, gross total resection, and wide resections including mutilating surgeries/amputations have all been described. Chemotherapeutic agents used have mostly included drugs effective against other aggressive pediatric sarcomas – Vincristine, Cyclophosphamide, Doxorubicin, and Etoposide [1,2,4].

Although individual case reports have been published describing infants with fibrosarcoma and coagulopathy, the association and its risk factors have not been reviewed and characterized to date. We therefore reviewed the published literature for reports of anemia, bleeding, or coagulopathy upon presentation of CIF. We found a total of 21 cases reported separately in 18 case reports (summarized in Table 1). Interestingly, all of the reported patients were very young, diagnosed within the first

2 months of life, and 4 even presented perinatally with hydrops fetalis. Fourteen had extremity tumors, and 7 had axial/trunk tumors. Anemia was present in all patients, thrombocytopenia was reported in 11, and 6 had other evidence of coagulopathy such as prolonged PT, aPTT, or low fibrinogen. Bleeding was a prominent feature in 6 patients, and resulted in death in 2 of them. Several were initially misdiagnosed as hemangioma and had been treated with steroids [8,10,13,15,16]. The 4 patients who presented with hydrops fetalis died shortly after birth and 2 other patients died of bleeding complications. The remaining 15 children did well: One patient received chemotherapy as the only modality of treatment, while 14 underwent surgical resection of the tumor, and 6 of the 14 also received chemotherapy. Of note, 6 of the 14 surgical procedures consisted of amputation.

While the pathophysiology of consumptive coagulopathy in CIF is unclear, similar findings in other vascular tumors are thought to be secondary to platelet consumption within the blood vessels [17]. This is typically defined as Kasabach-Merrit syndrome, which was initially described as thrombocytopenic purpura associated with a vascular lesion, characterized by hemolytic anemia, thrombocytopenia, and secondary consumptive coagulopathy [23,24]. A similar pathophysiology is likely to be responsible for the findings in CIF, due to the known high vascularity of this tumor.

One of our patients (patient #2) developed life-threatening hepatopathy as a complication of VAC chemotherapy. Hepatopathy and hepatic sinusoidal obstruction syndrome (previously called veno-occlusive disease of the liver) is a rare complication of chemotherapy, commonly associated with Vincristine and Actinomycin [25,26]. Younger infants have been reported to be at a higher risk of vincristine and actinomycin toxicity [27,28]. Indeed, in addition to our patient reported here, we found 6 other case reports of life-threatening liver toxicity after chemotherapy for CIF. All 6 had been receiving VAC chemotherapy, and 2 died as a consequence [13,16,29–32]. Thus, in patients with CIF who are younger than 2 years of age, this serious complication needs to be considered when making management decisions.

Conclusions

This report underscores the importance of considering CIF when evaluating a rapidly growing congenital vascularized mass, especially in neonates and infants presenting within the first 2 months of life. Bleeding may be a prominent feature of CIF in this age group, especially in patients with extremity tumors, and may be associated with a high mortality. The coagulopathy associated with this tumor may be manifested by anemia or thrombocytopenia, even in the absence of overt bleeding. When feasible, surgical excision, even with positive margins, can be associated with long-term tumor-free outcome. For non-resectable tumors or when mutilating surgery or amputation is contemplated, neo-adjuvant chemotherapy may help achieve tumor control with preservation of limb and function. Such patients may do well even without definitive local control, as demonstrated by the first patient in our report. VA and VAC regimens have both been reported to be successful; however, it is important to consider toxicities, specifically the risk of hepatopathy and hepatic sinusoidal obstruction syndrome in these young patients.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Abbreviations

aPTT – activated Partial Thromboplastin Time; **CIF** – congenital infantile fibrosarcoma; **FFP** – fresh frozen plasma; **PRBC** – packed red blood cell; **PT** – prothrombin time.

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