



Pancreatic Hemangioendothelioma in an Infant: Successful Conservative Management

Massimo Provenzi^{1*}, Carlo Foglia¹, Laura Cavalleri¹, Federica Bruni¹, Francesca Limido¹, Di Silvio Chiara¹, Annachiara Malvezzi¹, Valentina Privitera¹, Andrea Gianatti², Paola Tebaldi², Paolo Marra³, Lorenzo D'antiga⁴

¹Oncologia Pediatrica Ospedale Papa Giovanni XXIII, Bergamo, Italy

²Anatomia Patologica Ospedale Papa Giovanni XXIII, Bergamo, Italy

³Dipartimento Diagnostica per immagini Giovanni XXIII, Bergamo, Italy

⁴Centro di Epatologia, Gastroenterologia e Trapianti Pediatrici Ospedale Papa Giovanni XXIII, Bergamo, Italy

*Corresponding author: Massimo Provenzi, Oncologia Pediatrica Ospedale Papa Giovanni XXIII, Bergamo, Italy

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Abstract

Kaposiform hemangioendothelioma (KHE) is a rare aggressive childhood vascular neoplasm that may involve any part the body and rarely affects the pancreas. The association with consumptive coagulopathy, known as Kasabach-Merrit Syndrome (KMS), determines a potential life-threatening condition with up to 30% mortality rate. In most of the reported cases, surgery was necessary for both diagnosis and treatment. Herein we present the case of a 64 day-old girl referred to our pediatric emergency department for obstructive jaundice, coagulopathy and thrombocytopenia. Abdominal Ultrasound (US) and computed tomography revealed a hypervascular mass involving and subverting the entire pancreas. The baby underwent percutaneous US-guided needle biopsy that allowed to make the diagnosis of KHE; surgery was unfeasible due to the extent of the disease. The initial response was obtained with the combination prednisone, vincristine and Propranolol. The therapy was subsequently consolidated and strengthened by long-term treatment with sirolimus. Coagulopathy and obstructive jaundice resolved after two weeks of treatment. The patient is currently 10-month-old and is asymptomatic with normal blood tests. A follow up magnetic resonance imaging showed a marked shrinkage of the mass. In this case of advanced pancreatic Kaposiform hemangioendothelioma (KHE) medical therapy provided excellent clinical outcome and allowed to avoid resective surgery, which in infants is burdened by high risks of complications.

Introduction

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor that occurs mainly during infancy or early childhood. KHE is locally aggressive and it is potentially life-threatening when associated with a phenomenon known as Kasabach Merrit Syndrome (KMS), characterized by severe thrombocytopenia, microangiopathy, haemolytic anemia and consumption coagulopathy in the setting of a rapidly expanding vascular tumor [1,2]. KMS results from the intralesional platelet trapping and confers a high propensity to bleed. KHE may affect any organ, but visceral involvement is uncommon [3]. Pancreatic KHE is usually associated with obstructive jaundice, hepatomegaly, palpable mass and duodenal obstruction [4]. Ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) scanning guide the diagnosis [4]. The treatment of pancreatic KHE is dependent upon the clinical presentation [4]. To date,

no standardised treatment exists on KHE management, although surgical therapy, when feasible, is widely considered as the first choice. We report a severe case of pancreatic KHE complicated by KMS, successfully treated conservatively, with a multidrug therapy approach.

Case Report

A 2 months and 4 days old female infant was admitted to our emergency department for anorexia, irritability and acholic stools since two days. Physical examination showed adequate nutritional status, cutaneous and scleral jaundice and a periumbilical ecchymotic patch. Laboratory tests disclosed anemia (Hb 7.8 g/dl), thrombocytopenia (16 x10⁹/L), elevated liver enzymes (AST 156 IU/L, ALT 102 IU/L, and GGT 901 IU/L), elevated conjugated bilirubin (95 µmol/l), hypofibrinogenemia (86 mg/dl), elevated D-dimer (>35.000 ng/ml), INR 1.31 (n.v. 0.8-1.17), normal

amylase and increased lipase (320 IU/L). Abdominal US and CT showed a well-defined mass (7 cm x 4 cm) in the retroperitoneal space, involving and subverting the pancreatic gland. The mass was hyper-enhancing and determined encasement of the celiac and mesenteric vessels, with occlusion of the spleno-mesenteric confluence. Marked dilation of the biliary tract was also noted (Figure 1).

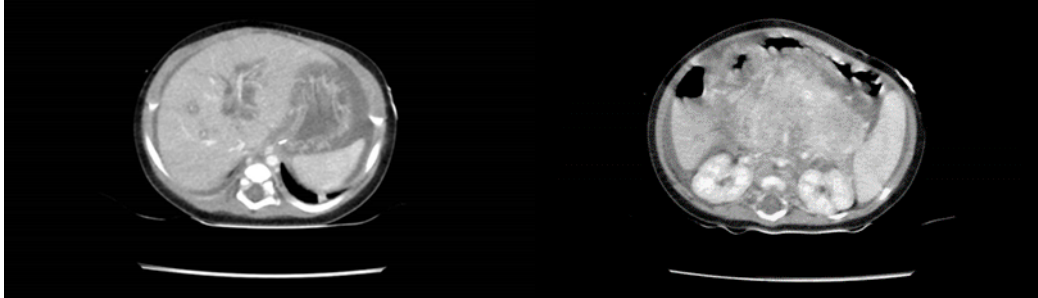


Figure 1: Axial computed tomography scan of the abdomen demonstrating the locally invasive pancreatic mass with dilation of the intrahepatic biliary tract.

A US-guided 18G core needle biopsy was performed (Figure 2). Immunohistochemistry staining demonstrated a Ki67 labeling index of 40%. The spindle cells were diffusely positive for vascular endothelial markers such as CD34 and ERG, and negative for HHV8. Smooth muscle actin (SMA) was negative. The areas comprising dilated lymphatic vessels showed negative staining with CD34, ERG, but positive for D240. The histological features and the immunophenotype (CD34 +, ERG2-40 +, actin and desmin -, chitokeratin AE1 AE3 -) were diagnostic for KHE. The procedure was complicated by hemoperitoneum managed with blood volume expansion and transfusions.

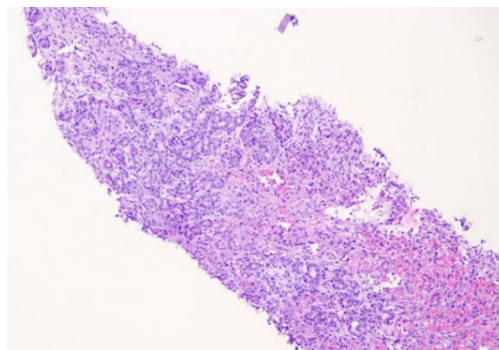


Figure 2: Hematoxylin-eosin staining shows infiltrating nodules of spindle cells forming a characteristic vascular pattern. The tumor nodules are composed by fascicles of spindle shaped endothelial cells and slit-like vascular channels. In addition, there are extravascular red blood cells, fibrin thrombi and dilated lymphatic vessels. There is mild nuclear variation, but no significant nuclear atypia, or necrosis, with rare mitoses.

Considering the patient's age, the size of the mass and the high risk of bleeding, we regarded surgical therapy as unfeasible because too risky. We therefore maximized medical therapy using a combination of drugs considered effective against KHE, in an attempt to quickly resolve the two main clinical problems: haemorrhagic coagulopathy and obstructive jaundice. An initial four-drug therapy regimen was introduced, followed by subsequent gradual suspension, comprising: 4-week therapy with prednisone at the dose of 5mg/kg for 7 days, then 2 mg/kg for 15 days followed by a slow tapering; a 6-week course of vincristine

(0,05 mg/kg/week); 6-months therapy with propranolol at the dose of 2 mg/kg/day in 4 doses; therapy with Sirolimus (0.05 mg/kg/day) modulated to maintain a blood concentration within the therapeutic range of 7,5-10 ng/ml, and scheduled to be continued for 2 years.

All the complications related to KPM and obstructive jaundice solved by two weeks after starting treatment (Table 1). In this period of time the patient required 7 RBC transfusions and 11 platelet transfusions, due to the presence of haemoperitoneum.

	ZENITH/NADIR	NORMALIZATION TIME AFTER STARTING THERAPY
Total Bilirubin	26,5	3 weeks
Platelets	16x10 ⁹ /L	4 weeks
GammaGT	901 IU/L	3 months
Lipase	334 IU/L	3 days
Amylase	Always normal	
Hb	5,5 g/dl	6 weeks
Coagulopathy		6 days
Fibrinogen	86 mg/dl	8 days
D-Dimer	>35.000 ng/ml	
Free Hb	29,9 mg/dl	

Table 1: Abnormal haematological values and normalization time after treatment start.

The first month of therapy has been complicated by sepsis due to *Candida Parapsilosis* and superinfection of the central venous catheter (which was removed and subsequently replaced). Overall, the patient manifested severe neutropenia only for 5 days. Currently the patient is 10 months old and she is in excellent conditions. She has shown a progressive weight gain and normal neurological development. The current haematological parameters are all within the normal limits. Magnetic resonance imaging assessment showed a marked shrinkage of the lesion that still extends to the entire pancreatic gland. Within the mass there is now a partial recovery of the pancreatic parenchyma, with the pancreatic duct recognizable in almost its entire course; a modest dilation of the biliary tree is still present. The spleno- -mesenteric and portal venous axes are patent (Figure 3).

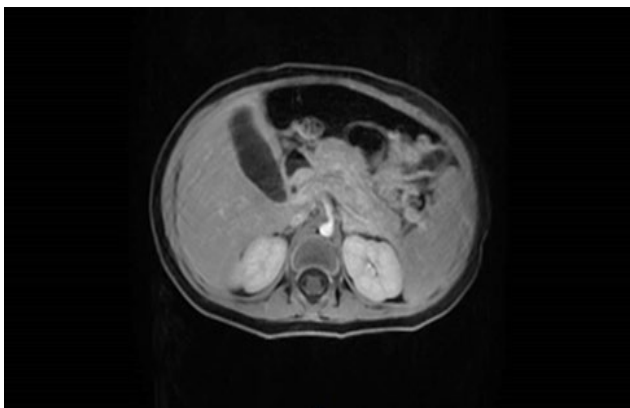


Figure 3: Magnetic resonance imaging scan of the abdomen shows decrease in the mass and improvement in pancreatic parenchymal representation, with regular caliber of the main pancreatic duct.

Discussion

Benign vascular tumors are not uncommon in pediatric patients and, after an initial size spurt, may undergo spontaneous involution or require medical management [2]. KMS is a life-threatening complication of large KHE, with high mortality risk related to the difficulty in bleeding control [5].

>Cutaneous KHE are more easily controlled and, when surgical removal is feasible and safe, the condition is easily resolved [4].

In our case, retroperitoneal localization, involvement of the entire pancreatic gland, severe KMS, obstructive jaundice, the age and small body size have challenged the management and increased remarkably the risks. Ultrasound and CT scan revealed a hypervascular solid mass involving the entire pancreas with encasement of the mesenteric vessels and compression on the biliary tract. Imaging was not conclusive for the final diagnosis that was reached only after percutaneous biopsy and clinical correlation with coagulopathy. The histological assessment is considered essential even in the case of strong suspicion. The ultrasound-guided core needle biopsy allowed to reach a definitive histological diagnosis but determined a life-threatening abdominal bleeding. Based on this experience we suggest to perform a surgical biopsy whenever possible, to minimize the risk of bleeding complications.

Table 2 summarises the cases of pediatric pancreatic KHE published previously. We found the description of only 11 patients who presented with pancreatic KHE, all but one younger than 1 year. Our patient is the youngest described so far, whereas the oldest was 3 year-old [3,6,7,8].

Number of patients	11
Gender:	
Male	5
Female	5
Age:	
< 2 months	0
2-12 months	10
>1 year	1
Mesenteric vessel involvement	4/11 (36%)
Jaundice	6/11 (54%)
Size:	
< 5 cm	3
> 5 cm	2
KMS	5/11 (45%)
Management:	

Conservative	3
Percutaneous biliary decompression	2
Vascular embolization	1
Choledochojejunal bypass	1
Surgery	1

Table 2: Features of reported cases of retroperitoneal kaposiform hemangioendothelioma (from ref).

KMS has been described in 50% of patients, and in all cases it is already present at diagnosis. The management of KHE complicated by KMP is challenging. When feasible, surgery is the definitive treatment, as it allows prompt normalisation of coagulopathy; nonetheless most lesions are unresectable because of patient features or location and size of the mass. Moreover, there is a high risk of bleeding [9]. In most of the cases reported in the literature, extended surgery such as Whipple’s procedure or hepatico-jejunostomy were performed to solve obstructive jaundice [3,6,7]. Only a few patients were treated with medical therapy alone. Based on our centre expertise on paediatric disease of the liver and biliary tract, we decided to maintain a conservative management, keeping the option of biliary drainage for a later stage, if required. A review of previous publications on the medical treatment of hemangioendothelioma showed that the main drugs used are steroids, vincristine, antiplatelet agents, propranolol and sirolimus (3,6,7,8,9) (Table 3). In recent years there has been a growing use of sirolimus, an immunosuppressive drug that forms a molecular complex binding to mTOR, inhibiting its function and resulting in blockage of the production of VEGF and proangiogenic cytokines [9].

Systemic drug	Dosage
Corticosteroids	Oral PDN 2 mg/kg or IV MPDN 1,6 mg/kg
Vincristine	IV 0,05/kg once weekly
Sirolimus	Oral 0,8 mg/m ² /dose twice daily, adjust for trough level of 8-15 mg/ml
Ticlopidine	Oral 10 mg/kg
Interferon alfa	Subcutaneous injection, 1-3 x 10 ⁶ U/m ²
Propranolol	Oral 2-3 mg/Kg

Table 3: Recommended pharmacologic therapies in pancreatic hemangioendothelioma, data reported in the literature (ref...).

The success rate of monotherapy is poor. The most commonly used drug combinations are steroid + vincristine and steroid + sirolimus (9). Due to the seriousness of the situation and the inability to use surgical therapy, we decided to use a combined medical therapy with 4 drugs, with the plan to progressively reduce the drug doses in the event of a positive response. In our

opinion, this choice favored a positive outcome with resolution of the two main clinical problems, haemorrhagic coagulopathy and obstructive jaundice, in about two weeks, even if the normalization of the main haematological parameters was slower (Table 1).

Treatment complications were relevant, but promptly resolved, and medical treatment was overall well tolerated by the patient. The girl is currently 10 months old and in good health. Although the pancreas was almost entirely replaced by neoplasia, the MRI performed at 6 months showed a progressive reduction of the mass (Figure 3). The patient is still on sirolimus monotherapy, which we plan to continue until the lesion will entirely shrink. It is described that the growing phase of deep hemangioendotheliomas can extended up to 12 months, and in some cases up to 24 months after stabilization; the regression phase is commonly completed in 60% of cases at 4 years and in 75% at 7 years.

In conclusion, childhood pancreatic KHE is an extremely rare vascular tumor with limited treatment options [3,6,7,8]. The experience made with this case was relevant for both extension and age, and it showed that a conservative management with a multidrug therapy schedule can be a good alternative to surgery.

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