

# Efficacy of Pegylated Lyposomal Anthracyclines and of Intra-Arterial Carboplatin and Doxorubicin Combined with Local Hyperthermia in a Case of Malignant Endovascular Papillary Angioendothelioma

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**Abstract:** Malignant vascular tumors are exceedingly rare in childhood. Generally, their prognosis is dependent from a microscopically complete surgical resection. We observed the case of a 4-year-old boy affected by malignant endovascular papillary angioendothelioma, a rare vascular tumor of intermediate malignancy, involving all his left leg and partially the pelvis. Its very large size hampered any surgical intervention. However, we could demonstrate high sensitivity of the tumor to lyposomal anthracyclines and the child was eventually cured by the intra-arterial administration of carboplatin and doxorubicin coupled with local hyperthermia. This experience probably represents the first step toward an effective treatment of malignant vascular tumors in infancy.

**Keywords:** Childhood, vascular tumors, endovascular papillary angioendothelioma, pegylated anthracyclines, doxorubicin, carboplatin, intra-arterial administration, hyperthermia.

## INTRODUCTION

Malignant endovascular papillary angioendothelioma (EPA) is a rare vascular tumor that more often occurs in children and young adults. Since its first description in 1969 by Dabska *et al.* [1] only 30 cases about have been reported in the literature and 19 out of them were children [2, 3].

In many cases the tumor remains confined to the dermis, the structure more often originally involved, but it is also able to invade deeper structures such as bone and tendons and to metastasize to regional lymph nodes. It usually appears as an intradermal, painless mass of few centimeters in diameter but occasionally reaches greater dimensions showing elevated and firm margins and surface ulcerations.

From data reported in literature complete surgical excision seems to be the only suitable form of therapy; in fact radiotherapy, when used, did not achieve any result and chemotherapy has never been tried.

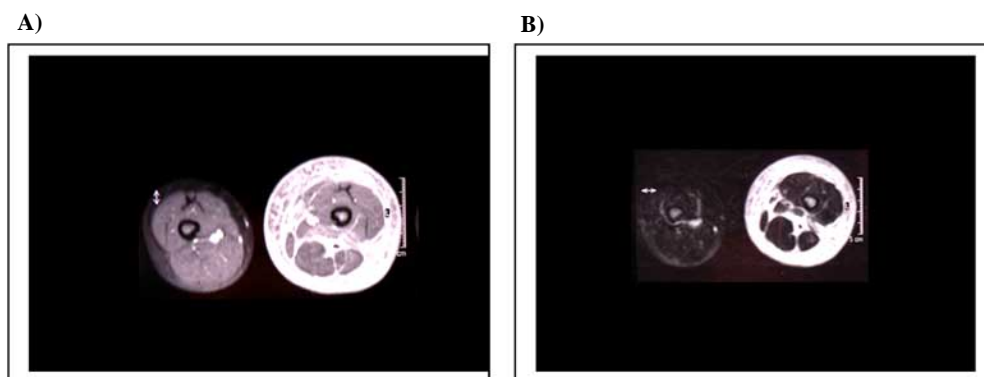
We report here the case of a 4-year-old boy with a very large Dabska tumor entirely affecting his left leg and partially the pelvis. Therefore, he could not be submitted to surgical management but was treated by systemic pegylated lyposomal doxorubicin and finally by intra-arterial chemotherapy including carboplatin and doxorubicin and achieved complete remission that lasts until now, three years and eight months after the onset.

## CASE REPORT

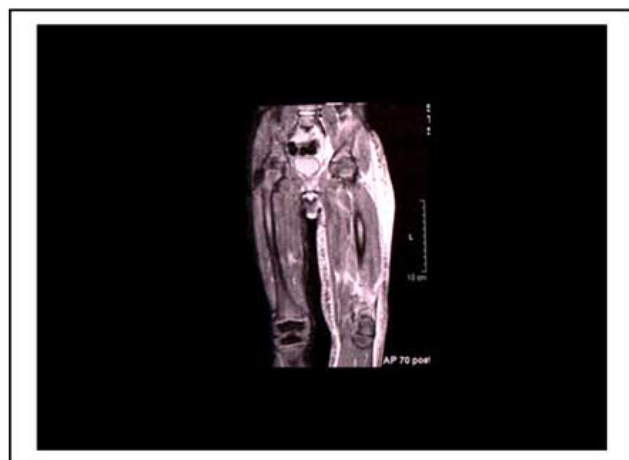
The patient, a 4-year-old boy was admitted to our Department in January 2004 with a 3-month history of a progressive, painless swelling of his left leg, first noticed and described as an ecchymotic oedema of the anterior face of the thigh.

On admission his general condition was good. Physical examination showed a firm, painless, violaceous swelling involving all his left lower limb, from the corresponding buttock to the ankle, measuring about 50 centimeters in length. Moreover, left thigh measured 38 centimeters in diameter at groin (vs 31 cms right thigh), 36 centimeters in the middle (vs 27 cms), 31 centimeters just over the knee (vs 22 cms). Other abnormal clinical findings were not found. At the initial evaluation pertinent normal laboratory results were obtained. Chest radiograph, skeletal x-ray survey, <sup>99m</sup>Tc bone scan, ultrasonography of the abdomen, Doppler ultrasonography of the lower limbs were all negative. Magnetic resonance imaging (MRI) of the legs revealed thickening of the soft tissues involving the entire left limb; the extensive lesion was hypointense and contrast enhancing on T1-weighted spin echo images and hyperintense with a lobular pattern on T2-weighted spin echo images (Figs. 1A, 1B, 2). An excisional biopsy was performed. Histologic examination revealed a vascular tumor characterized by a brisk proliferation of irregular vascular channels with endovascular endothelial cell papillary proliferations. Cytologic atypia was seen. Immunohistochemically the majority of tumor cells were strongly positive for vimentin and CD31, weakly positive for factor VIII-related antigen. The above histologic findings were consistent with a diagnosis of EPA.

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**Fig. (1).** Contrast-enhanced MR T1-weighted image showing that the tumor entirely encompasses **A)** the left thigh and **B)** the left leg, involving subcutaneous soft tissues and fibroadipose intermuscular septa.



**Fig. (2).** The tumor involves the whole limb and also enters the pelvis through the groin, along with the iliac vessels, reaching the left of the bladder.

Because of its size the tumor was not amenable to surgical treatment without unacceptable mutilation. Therefore, we decided to treat the child as if he was affected by Kaposi's sarcoma and to use liposomal doxorubicin [4]. From March to June 2004 the patient received five courses of liposomal pegylated doxorubicin 20 mg/m<sup>2</sup> as a 8 h infusion for 1 day, administered every two weeks. At the end of May 2004 a repeat MRI revealed a good reduction in thickness of most of the above mentioned lesion (Fig. 3). We then tried to consolidate this partial remission by the administration of drugs other than doxorubicin. Between June and November 2004 the child received six courses of dacarbazine 200 mg/m<sup>2</sup> as 1 h infusion plus vincristine 1.5 mg/m<sup>2</sup> infused slowly for 1 day and dactinomycin-D 1.5 mg/m<sup>2</sup> infused slowly plus etoposide 150 mg/m<sup>2</sup> as a 1 h infusion for 1 day; courses were administered alternatively every 3-4 weeks. However, in December 2004 we had to document progression of the tumor. Repeat three courses of liposomal pegylated doxorubicin failed to achieve any significant result.

Taking into account the good results reported in patients with extremity osteosarcoma receiving intra-arterial car-

boplatin as a single agent [5] and in patients with soft tissue sarcomas of the extremities receiving intra-arterial doxorubicin [6], we turned to loco-regional chemotherapy combined with regional hyperthermia [7].



**Fig. (3).** May 2004. Great reduction of the thickening of the soft tissues after liposomal anthracyclines therapy.

A catheter was inserted percutaneously through the femoral artery using the Seldinger technique, and its tip positioned into the iliac artery; the leg was warmed up to about 40°C by an electric blanket rolled around. By this way doxorubicin was given for two consecutive days at a daily dose of 20 mg/m<sup>2</sup> by continuous infusion and carboplatin 600 mg/m<sup>2</sup> diluted in 500 cc of normal saline was infused over 2 h for one day. From March 2005 and March 2006 the child received seven courses of chemotherapy, three of doxorubicin and four of carboplatin, given alternatively with 6-8 weeks intervals. A progressive reduction of the tumor was observed in July and November 2005 and finally the complete remission was documented in July 2006 (Fig. 4A, 4B), that lasts until now, September 2007, three years and eight months after the diagnosis and fourteen months after the achievement of complete remission. The child is now in good health, has no limitations in motion or in his daily activities. Cardiac evaluation has been regularly performed according to the guidelines for cardiac monitoring during

A)



B)



**Fig. (4).** July 2006. Complete remission of the tumor and normal feature **A)** of the thigh and **B)** of the leg.

and after anthracycline therapy of the CCSG [8], and up to now no sign of cardiotoxicity has appeared.

## DISCUSSION

EPA is classified, together with malignant hemangioendothelioma (HE) and Kaposi's sarcoma, as vascular tumor with intermediate or borderline malignancy [9]. These tumors are extremely rare in children. Paucity of data makes uncertain prognosis and treatment strategies. However, from the few data available, it seems that the outcome of these patients is mainly dependent from the size of the primary lesion and the ensuing probability of achieving a microscopically complete surgical resection. In the series of six children originally reported by Dabska four out of them had a tumor of five centimeters or less in diameter and could be excised without additional therapy. However, one of these patients died later of metastatic disease. Three out of the five children affected by EPA reported by Fanburg-Smith *et al.* in 1999 [10] had a tumor less than five centimeters in diameter, went to surgical intervention and were alive without disease after a long follow-up. However, the other two cases, one with a tumor of undefined size and the other with a very large lesion of 40 cms or more, were lost to follow-up. In the series of four malignant HE, recently reported by the Italian and German Soft Tissue Cooperative Group (IGSTCG) [11], the only patient who survived had a tumor of five centimeters which was completely resected.

As it concerns systemic chemotherapy, this treatment has never been used in reported cases of Dabska tumor. In cases of malignant HE, when the tumor had not been completely resected, it failed to prevent local recurrence or the occurrence of distant metastases [11,12].

Radiation therapy has been used as front-line treatment in two of the six children reported by Dabska, but in both cases surgical excision was eventually done. Radiotherapy was also used in an adjuvant setting in three of the four patients with malignant HE reported by the IGSTCG, delivered at a high dose (60/65 Gy), but the two children who have had an

incomplete resection progressed and eventually died of disease. The only patient with diffuse malignant HE described by Lezama-del Valle [12] received radiation therapy without success and died of disease.

Our experience with the above described case of papillary angioendothelioma is unique and probably represents the first step toward an effective treatment strategy for vascular tumors in children. Likely, the lesion presented by our patient represents the largest vascular tumor described until now in children, among EPA but also among other tumors such as angiosarcomas, malignant hemangioendotheliomas or Kaposi's sarcomas. Not taking into account its intrapelvic portion, the tumor measured 50 x 35 centimeters, corresponding to about 0.17 square meters of surface area, that is to about one fourth of the whole body surface area of the child. Therefore, any surgical or radiotherapeutic approach was ruled out. However, this case clearly demonstrates that EPA is sensitive to anthracycline systemic chemotherapy, at least delivered as liposomal formulation in front-line chemotherapy.

The results reported in literature about two drugs, doxorubicin and carboplatin administered intra-arterially in cases of soft tissue sarcomas [6] and in cases of osteosarcomas [5], were encouraging. In the first study the authors administered to eleven patients with locally advanced soft tissue sarcoma doxorubicin as continuous intra-arterial infusion. They reported a response rate of over 90% and an overall survival rate of about 45% with a median follow-up of 120 months. Moreover, carboplatin was tested as single agent in the treatment of recurrent or refractory osteosarcoma [6]. It was administered intra-arterially to thirty-three consecutive patients and a favourable clinical response was documented in 80% of cases. Finally, hyperthermia has been shown to increase the activity of pegylated liposomal doxorubicin [7]. Owing to the above experiences we treated our patient in disease progression by the intra-arterial administration of carboplatin and doxorubicin combined with local hyperthermia as described above, obtaining a progressive reduction and finally a complete remission of the tumor.

We believe that our experience, although anecdotal, is worthy of note and that intra-arterial carboplatin and doxorubicin, when feasible, have to be tried in malignant endothelial vascular tumors of childhood.

#### ABBREVIATIONS

- EPA = Malignant Endovascular Papillary Angioendothelioma  
 MRI = Magnetic Resonance Imaging  
 HE = Malignant hemangioendothelioma  
 IGSTCG = Italian and German Soft Tissue Cooperative Group

#### ADDENDUM

Since the paper has been submitted for publication the child remains in continuous complete remission and in good health until now, September 2008.

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