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5-YEAR DISEASE-FREE SURVIVAL AFTER RESECTION OF MALIGNANT PEDIATRIC PHEOCHROMOCYTOMA WITH INFILTRATION OF INFERIOR VENA CAVA

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ABSTRACT

Pheochromocytomas are tumors arising from chromaffin cells, mainly of the adrenal gland, that synthesize, store, metabolize, and usually but not always secrete catecholamines . Most are benign and curable by surgical resection, but some are clinically malignant. There are no reliable histopathological methods for distinguishing benign from malignant tumors. Instead, malignancy requires evidence of metastases at non-chromaffin sites distant from that of the primary tumor.

We present a case of 13 year old boy with malignant pheochromocytoma on abdominal CT infiltrating right kidney and IVC, and interrupted caval flow

After preoperative preparation with alpha end beta blockers the patient underwent en bloc resection of the right kidney and adrenal gland and tangential resection of the IVC.

Postoperative follow-up included yearly whole body CT and urine and plasma catecholamines and metanephrines. At 5-th year after the operation the patient is disease free.

Because metastases may be microscopic at the time of initial surgery, there is accumulating evidence that continued screening may be most important in patients with pheochromocytoma judged by existing histopathological criteria to be at risk for malignancy.

Key words: adrenal tumor, pediatric hypertension ,

INTRODUCTION

Pheochromocytomas are tumors arising from chromaffin cells, mainly of the adrenal gland, that synthesize, store, metabolize, and usually but not always secrete catecholamines (1). Most are benign and curable by surgical resection, but some are clinically malignant (2). Although the prevalence of malignancy is commonly cited at about 10%, other estimates suggest rates of between 5–26% depending on how malignancy is defined, with lower or even higher values in certain patient groups depending on the underlying mutation (3, 4, 5).

There are no reliable histopathological methods for distinguishing benign from malignant tumors. Instead, malignancy requires evidence of metastases at non-chromaffin sites distant from that of the primary tumor. Although extensive invasion of adjacent tissues can be considered an indicator of malignant potential, local invasiveness and malignant disease are not necessarily associated. The presence of metastases provides the only currently widely accepted means to define malignant pheochromocytoma (6).

Because pheochromocytoma is more common in adults than in children, most of the data available on its behavior and management have been based on adults, and thus the etiopathogenesis and management of pediatric pheochromocytoma remains obscure (7). There are some differences in behavior of pheochromocytoma between the pediatric and adult populations. Most studies have confirmed male preponderance and greater tendency for familial occurrence and multi-focality (43% in children vs. 30% in adults), an increased incidence of extra-adrenal tumors (30-40% in

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children vs. 10% in adults), and similar/lower risks of a malignant pheochromocytoma (3.5%) (8,9). The mean 5-yr survival rate for malignant pheochromocytomas is about 40%(10,11).

CASE REPORT

A 13 year old boy was admitted to our institution for surgical treatment of pheochromocytoma of the right adrenal gland. The tumor was misdiagnosed as hydatid cyst of the liver, and the patient has undergone exploratory laparotomy in other institution, followed by complicated postoperative period in which the patient developed acute lung edema. After dehospitalisation the patient was prepared by pediatric team for operation with alpha and beta blockers.

On admission the patient was in good somatic condition, normotensive and normofrequent. His laboratory data was within normal ranges except of extremely elevated vanillyl mandelic acid, total catecholamines, and metanephrines. Preoperative work-up included abdominal CT on witch tumor infiltrated right kidney and IVC, and interrupted caval flow **(fig. 1, 2).** The patient was scheduled for right adrenalectomy with nephrectomy and resection of the IVC.

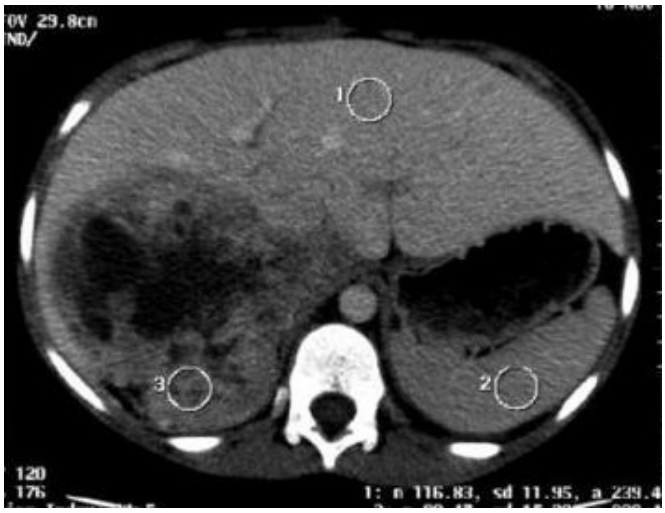

Fig. 1. Preoperative CT

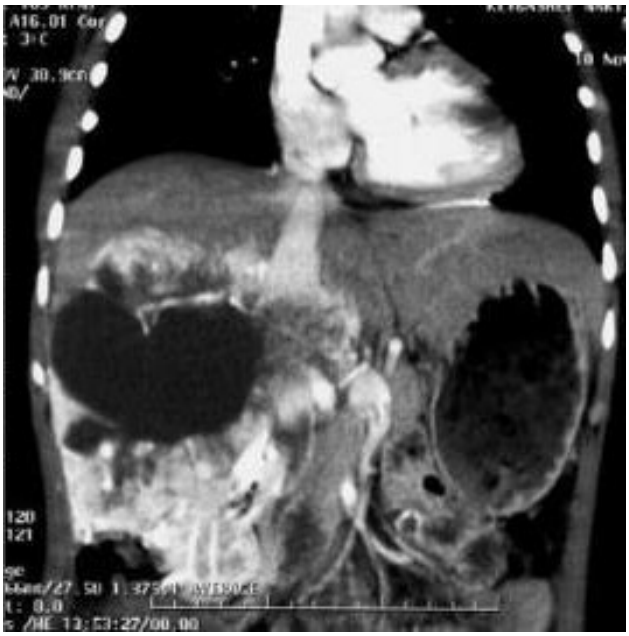

Fig. 2. Preoperative CT

A standart right J-shaped incision was used. The tumor was dissected from the visceral surface of the liver. Then the anterior wall of the IVC was dissected up to the hepatocaval confluence. Retrohepatic supratumoral control of the IVC was achieved. Tumor was resected with tangential caval resection en bloc with right kidney and adrenal gland. **(fig. 3, 4, 5)**

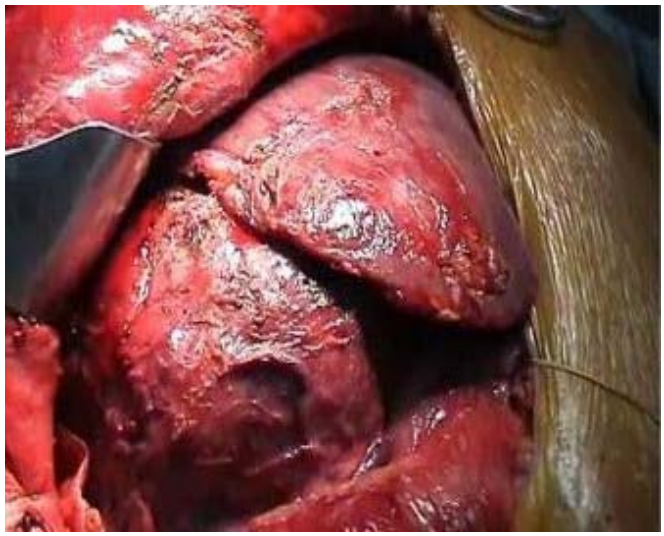

Fig. 3. The pheochromocytoma in situ

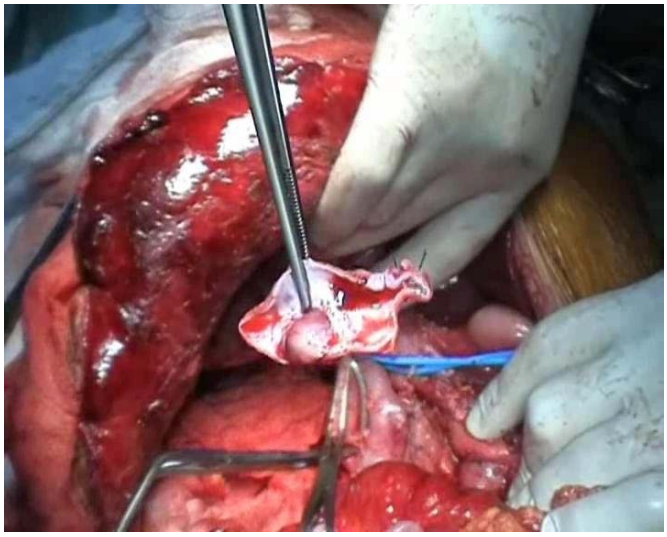

Fig. 4. Tumor thrombi in IVC

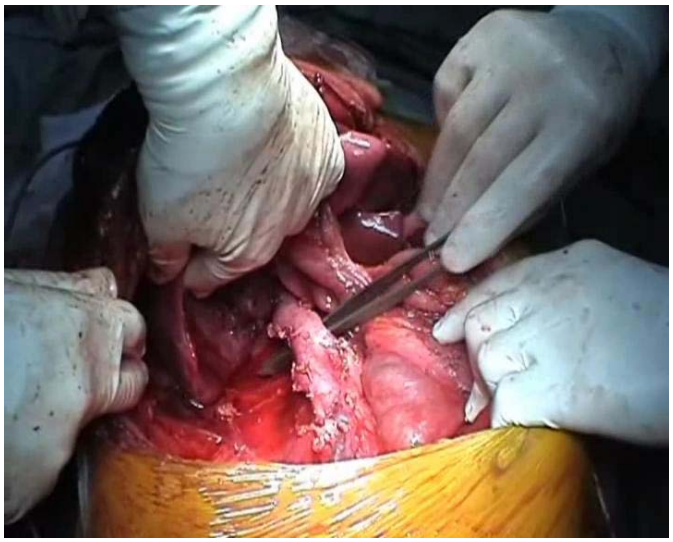

Fig. 5. IVC after tangential resection

Postoperative period was uneventful. Postoperative follow-up included yearly whole body CT and urine and plasma catecholamines and metanephrines. At 5-th year after the operation the patient is disease free.

DISCUSSION

Malignant pheochromocytoma is rare in childhood and the prognosis of this tumor in children is not well known. Presenting signs, the localizations of the primary tumor or of metastases, and the course of malignant pheochromocytoma in children do not seem to be significantly different from those in adults . In cases of malignant pheochromocytoma, multimodality treatments can be used. However, the benefits of chemotherapy, 131I-MIBG therapy, external radiation and octreotide remained undetermined. The mean 5-yr survival rate for malignant pheochromocytomas is about 40% (10, 11). Metastatic disease in pheochromocytoma may be present at the time of initial diagnosis or may only become evident after surgical removal of the primary tumor, usually within 5 years, but sometimes 16 or more years later (12, 13, 14).

There is evidence that molecular markers, such as expression of human telomerase reverse transcriptase and heat shock protein 90 (HSP90) (15, 16), might provide alternative methods for distinguishing malignant from benign pheochromocytoma. Other possible molecular markers include secretogranin II-derived peptide (17) and numerous factors associated with angiogenesis (18, 19, 20, 21, 22). Thomas Giordano indicated that a truly reliable predictor of malignant behavior would likely only be achieved through use of a combination of molecular markers. The availability of a transcriptional signature for malignant pheochromocytoma and paraganglioma derived from gene expression profiling studies might permit development of diagnostic tests for this purpose (23).

Without treatment the 5-year survival is generally less than 50% (24). The course, however, can be highly variable with occasional patients living more than 20 years after diagnosis (25).

Once malignancy is diagnosed, therapy is generally directed at controlling blood pressure, but may also include tumor debulking. Hypertension and catecholamine-dependent symptoms can be controlled with a-adrenergic receptor blockade followed by b-adrenergic receptor blockade. Levels of circulating norepinephrine in patients with extensive disease can be extraordinarily high. In such patients consideration should be given to the potentially cytotoxic effects of catecholamines on the myocardium. Inhibition of catecholamine synthesis with a-methyl paratyrosine (Demser) in exceptional circumstances may be useful in patients with high circulating levels of catecholamines (26, 27). The significant side-effect profile of a methylparatyrosine, however, limits the dosage and duration of therapy.

Surgery for malignant pheochromocytoma is rarely curative, but resection of a primary mass or metastases can reduce exposure of the cardiovascular system and organs to toxic levels of circulating catecholamines (28). Surgery may also be appropriate for lesions present in life-threatening or debilitating anatomical locations (29). Surgical debulking may also be used before radio- or chemotherapy, but whether this offers any true benefits has not been assessed by any randomized prospective trial. Alternatives to surgical resection include external beam radiation, cryoablation, radiofrequency ablation, transcatheter arterial embolization, chemotherapy, and radiopharmaceutical therapy (30, 31). Chemotherapy with a combination of cyclophosphamide (Cytoxan), vincristine (Oncovin), and dacarbazine (DTIC-Dome) provides partial remission and improvement of symptoms in up to 50% of patients with malignant pheochromocytoma (32). Usually, however, improvement only lasts for 1 to 2 years. Radiopharmaceutical therapy, using high doses of 131I-meta-iodobenzylguanidine (131I-MIBG), which is transported into the cell via the cell membrane norepinephrine transporter present on most neoplastic chromaffin cells, provides an alternative palliative therapy that can also be effective in temporarily reducing tumor burden and symptoms.

Because metastases may be microscopic at the time of initial surgery, and therefore may not present as malignant disease until many years later, biochemical screening should continue at yearly intervals (12, 13, 14). however, there is a lack of consensus regarding the duration of follow-up and in what form follow-up screening should take. Some have indicated that biochemical testing alone is insufficient and that follow-up examinations should include imaging studies (32). Although it is generally agreed that follow-up should be long-term, it has recently been suggested that follow-up may not be necessary for all patients

with a resected solitary tumor (4). Certainly the accumulating evidence indicates that continued screening may be most important in patients with paragangliomas or tumors judged by existing histopathological criteria to be at risk for malignancy.

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