Case Report

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Malignant rhabdoid tumour of the liver in a seven-month-old female infant: A case report and literature review

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SUMMARY

Malignant rhabdoid tumours in children are rare and aggressive neoplasms that occur most commonly in the kidney. Extra-renal malignant rhabdoid tumours are even rarer and have been reported in the central nervous system (atypical teratoid/rhabdoid tumour) and other sites including the liver. To date fewer than 40 cases have been reported in the literature. Here we present a case of a 7-month-old female infant with a primary malignant rhabdoid tumour of the liver and review this entity as it compares to other cases reported in the literature.

Key words: Liver, neoplasm metastasis, rhabdoid tumour, survival rate

INTRODUCTION

Malignant rhabdoid tumours (MRT) in children are rare and aggressive neoplasms that occur most commonly in the kidney. Extra-renal malignant rhabdoid tumours (ERMRT) are even rarer and have been reported in the central nervous system (atypical teratoid/rhabdoid tumour) and other sites including the liver. The first description of these tumours was in 1978 when they were thought to be a rhabdomyosarcomatoid variant of Wilm's Tumour[1] because of their morphological similarity to rhabdomyoblasts. In 1982 Gonzalez-Cruzi and others[2] designated them as a distinct entity.[3,4] To date, there are fewer than 40 cases of malignant rhabdoid tumour of the liver reported in the literature. Here we describe a case of primary hepatic rhabdoid tumour in a child and review this entity reported in the literature.

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CASE REPORT

A 7-month-old female with no significant past medical history presented to an outside hospital with an 8-day history of fever, abdominal pain, poor oral intake, and clay-coloured stools. She was noted to have right upper quadrant tenderness and underwent an abdominal ultrasound that showed an intra-abdominal mass. An abdominal CT scan showed a heterogeneous mass in the right hepatic lobe with central fluid that measured 7.4 × 6.5 × 5.5 cm. Initial lab results showed a mild anaemia and thrombocytopenia and an alanine aminotransferase (ALT) of 86 (ref. 12-41), aspartate aminotransferase (AST) of 102 (ref. 22-63), and an alkaline phosphatase of 286 (ref. 60-330). Alpha-fetoprotein (AFP) was 192 ng/mL (reference for age, 0.8-87 ng/mL[5]) and hcG was 0.5 miU/mL. A CT-guided biopsy demonstrated malignant rhabdoid cells. Further workup including bone marrow biopsy, PET scan, CT of the thorax, and brain MRI did not reveal any evidence of metastatic disease and confirmed this to be a liver primary. She received two cycles of chemotherapy following the COG study EREN 0321 regimen. Her first course consisted of cyclophosphamide, vincristine, doxorubicin and her second cycle was carboplatin, cyclophosphamide, and etoposide. She was then transferred to our institution for definitive management including evaluation for transplantation.

Repeat CT showed the lesion was now 11.4 × 7.8 × 7.7 cm [Figure 1]. The decision was made to proceed with a right trisegmentectomy of liver segments 6, 7, and 8 which was received by our department. The gross specimen consisted of a 719 g right liver lobe resection. The cut surface revealed a firm, tan-white, heterogeneous mass with areas of haemorrhage that measured 13.0 × 10.0 × 5.0 cm [Figure 2]. Microscopically, the tumour consisted of large, polygonal rhabdoid cells with eccentric vesicular nuclei, prominent nucleoli, abundant cytoplasm, and juxta-nuclear eosinophilic, PAS-positive hyaline inclusions [Figure 3]. The tumour was positive for cytokeratin and CD99 and negative for BAF47/INI-1,

AFP, cyclin D1, and Hep Par-1 [Figure 4]. Chromosome microarray analysis was significant for a large interstitial loss of chromosome 22 between bands 22q11.21-q12.1.

The patient was discharged and was to receive follow-up care closer to home. Three months postsurgery she developed local disease recurrence and metastases to her lungs and was receiving palliative care from home. Five months postdiagnosis she died from her disease.

DISCUSSION

MRT's are rare and aggressive neoplasms that typically afflict the paediatric population and generally originate in the kidney. ERMRT's are even rarer and impart the same poor prognosis as their renal counterparts. Despite advances in diagnosis and treatment it remains a universally deadly disease. The median age at diagnosis reported in the literature is anywhere from 11 to 16 months,[3,4] and most patients are less than 2 years of age[6] with a similar male: female gender ratio. Recently, several reports have noted improved survival citing surgery and adjuvant chemotherapy as the reason. Marzano *et al*.[7] reported a case of primary hepatic MRT in a young adult with disease-free survival of 31 months and overall survival of 48 months. Jayaram *et al*.[8] reported on a case of a 3-year-old male who underwent liver transplantation because of an unresectable hepatic MRT. Three years post-transplant with chemotherapy [ifosfamide, carboplatin, etoposide (ICE)], the patient was still disease-free. Unfortunately, these cases are the exception, rather than the rule. Sibileau *et al*.[4] note that mean survival remains 15.3 weeks with an overall mortality rate of 89%.

Recently the hSNF5/INI1/BAF47 tumour suppressor gene on chromosome 22q11.2 was implicated in the tumourigenesis of MRT's and atypical teratoid/rhabdoid tumours.[9,10] Loss of this tumour suppressor gene, particularly in paediatric patients, is frequently noted. As such, a lack of INI1 protein expression by immunohistochemistry is a characteristic finding. Our case demonstrates this nicely.



Figure 1: CT image demonstrating liver mass

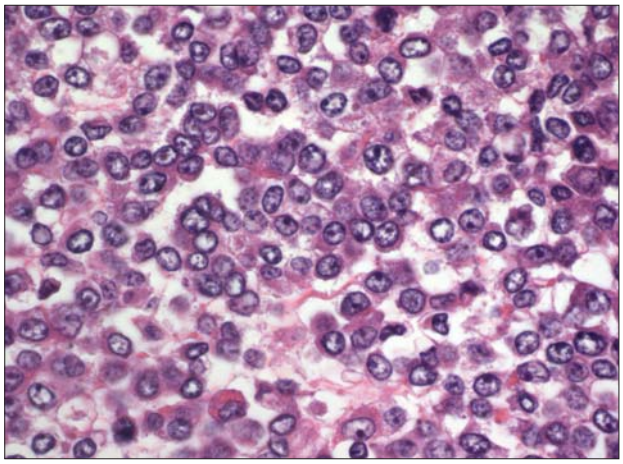


Figure 3: H & E image (10×) with PAS-positive cytoplasmic inclusions

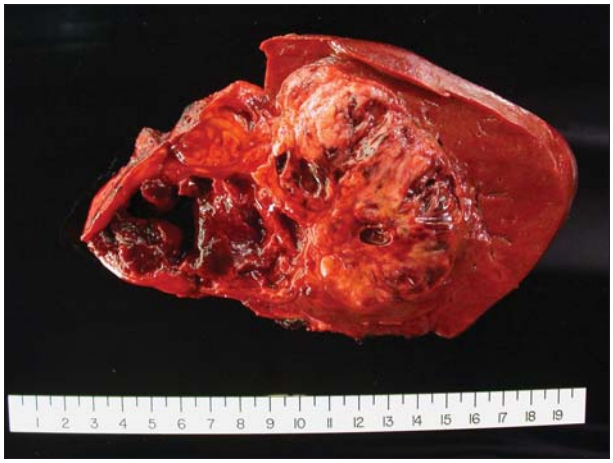


Figure 2: Gross image of tumour demonstrating extensive growth, necrosis, and relationship to adjacent normal liver parenchyma

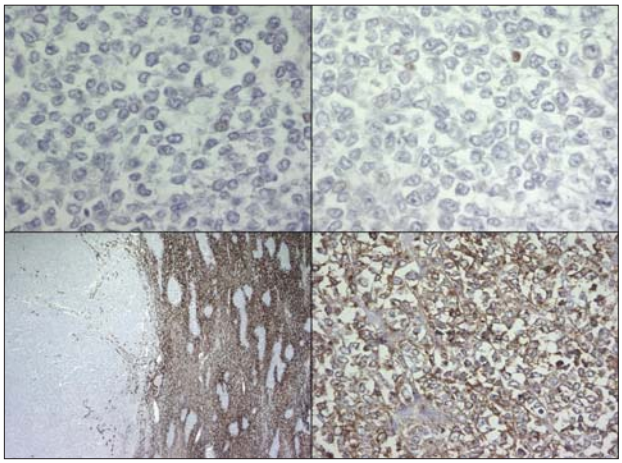


Figure 4: (clockwise from top left). Alpha-fetoprotein Immunohistochemistry (10×); BAF47/INI-1 Immunohistochemistry (10×) demonstrating loss of expression; HepPar-1 immunohistochemistry (2×), tumour (left) and normal liver (right) interface; CD99 immunohistochemistry (10×)

Table 1: Patient characteristics and outcome

Patient	Age at diagnosis	Sex	Metastatic disease	AFP (ng/mL)	INI1 status	Treatment	Outcome
1	0 months	M	Skin	WNL	Unknown	None	Died at 4 days
2	3 months	F	Pleural effusions	Unknown	Unknown	Chemotherapy and resection	Died of disease 8 months post-diagnosis
3	3 months	M	Bone marrow	WNL	Unknown	Carboplatin, vincristine, and epirubicin with resection	Died of disease 4 months post-diagnosis
4	3 months	M	Lung	13,381	Negative	Carboplatin, cisplatin, and doxorubicin	Died of disease 3 months post-diagnosis
5	3 months	M	Lung	14	Unknown	Cisplatin, 5-fluorouracil, vincristine, and doxorubicin	Died 2 months post-diagnosis
6	3 months	M	No	Unknown	Negative	Unknown	Died at 1 month
7	3 months	M	No	WNL	Unknown	Chemotherapy	Died 5 days after diagnosis
8	4 months	M	Lung	Unknown	Unknown	Cisplatin, 5-fluorouracil, vincristine, and doxorubicin × 1 course	Died of disease at 1 month
9	5 months	F	No	WNL	Unknown	Vincristine and cisplatin and complete resection	Died of disease 5 months post-diagnosis
10	6 months	F	No	Unknown	Negative	Chemotherapy	Alive at 17 months
11	6 months	F	No	Unknown	Unknown	Cisplatin, etoposide, and doxorubicin; gross total resection with positive margins	Died of disease 7 weeks post-diagnosis
12	6 months	F	Lung	Unknown	Unknown	None	Died of disease 0.4 months post-diagnosis
13 (Index case)	7 months	F	No	192	Negative	Chemotherapy (COG study EREN 0321 regimen) and gross total resection	Died of disease 5 months post-diagnosis
14	7 months	M	No	Unknown	Unknown	ICE × 3 courses, low-dose methotrexate with complete resection	Died of disease at 5 months
15	7 months	M	Lung	Unknown	Negative	Unknown	Died at 4 months
16	8 months	M	Lung	WNL	Unknown	Ifosfamide, vincristine, and actinomycin with resection of liver mass	Died at >15 months post-surgery
17	8 months	M	No	23	Negative	ICE × 10 cycles and right lobectomy	Died of disease 6 weeks after recurrence
18	8 months	M	Lung	WNL	Unknown	None	Died of disease
19	9 months	F	Pleural effusion	WNL	Unknown	Cisplatin, etoposide, and doxorubicin	Died 14 days post-diagnosis
20	10 months	F	Lung	Unknown	Unknown	Cisplatin, etoposide, and doxorubicin	Died of disease at 2 weeks
21	10 months	M	No	28.7	Negative	ICE and VAdriaC	Died of disease 2 months post-treatment
22	11 months	M	Lung	WNL	Unknown	Chemotherapy	Died of disease 8 weeks post-diagnosis
23	12 months	F	IVC, RA, lung	Unknown	Negative	VAdria C × 5 cycles, ifosfamide/ etoposide × 7 months and partial resection RA component	Alive 26 months from diagnosis
24	12 months	F	Lung	1,208	Unknown	Cisplatin, cyclophosphamide, and doxorubicin with hepatic artery embolization	Died 3 weeks post-diagnosis
25	12 months	M	Lungs, omentum	Unknown	Unknown	Actinomycin	Died at 1 week
26	13 months	F	Porta hepatis lymph node	WNL	Unknown	Ifosfamide, vincristine, and actinomycin × 6 months and gross total resection	Alive 6 years post-resection

Table 1: Cont.

Patient	Age at diagnosis	Sex	Metastatic disease	AFP (ng/mL)	INI1 status	Treatment	Outcome
27	16 months	F	Hilar lymph nodes	"Raised"	Unknown	Carboplatin and doxorubicin	Died at 2 months
28	17 months	M	CNS, lung	Unknown	Unknown	ICE with resection of liver mass and debulking of CNS mass	Died of disease 11 months after diagnosis
29	17 months	F	No	WNL	Unknown	Chemotherapy and radiation	Died of disease 6 weeks post-diagnosis
30	18 months	M	Lung	WNL	Negative	VAdriaC × 5 cycles, cyclophosphamide/carboplatin/ etoposide × 5 cycles	Died of disease 8 months post-diagnosis
31	21 months	M	Lungs, lymph node	20	Unknown	Cisplatin/5-fluorouracil/vincristine, ICE, VAdriaC, high-dose chemotherapy (etoposide/carboplatin/ cyclophosphamide; melphalan/ cyclophosphamide) with two autologous transplants	Died of disease 9 months post-diagnosis
32	36 months	M	No	WNL	Negative	ICE and VAdriaC and liver transplantation	Alive 3 years post-transplant
33	60 months	F	Hepatic artery	Unknown	Unknown	Cisplatin, 5-fluorouracil, vincristine, and doxorubicin	Died of disease 4 months post-diagnosis
34	84 months	F	Lung	WNL	Unknown	Carboplatin, vincristine, and epirubicin	Died 22 days post-diagnosis
35	180 months	M	No	Unknown	Negative	Ifosfamide, vincristine, actinomycin × 6 cycles; doxorubicin, cisplatin; radiation; and etoposide	Died 44 months post-diagnosis
36	324 months	M	No	WNL	Highly suggestive' of biallelic mutation	Left hepatectomy; 'sarcoma' chemotherapy	Alive 41 months from diagnosis

ICE= ifosfamide/carboplatin/etoposide; VAdriaC= vincristine/adriamycin/cyclophosphamide; CNS= central nervous system

Primary malignant liver tumours in children are uncommon. Hepatoblastoma accounts for over 90% of the primary malignant liver tumours diagnosed in the first 5 years of life[3] and has a similar presentation to hepatic MRT's. A sarcoma should be considered if hepatoblastoma and hepatocellular carcinoma are excluded. Primary sarcomas to consider are angiosarcoma, epithelioid hemangioendothelioma, liposarcoma, leiomyosarcoma, carcinosarcoma, fibrosarcoma, rhabdomyosarcoma, malignant solitary fibrous tumour, malignant fibrous histiocytosarcoma, undifferentiated embryonal sarcoma, and ERMRT. Routine histology should allow the distinction between these entities, but diagnosis can often be difficult. The presence of the characteristic mutation of the hSNF5/INI1/BAF47/SMARC gene (reflected by the lack of immunohistochemical expression of the INI1 protein by immunohistochemistry) can be helpful. Approximately 15-30% of rhabdoid tumours reported in the literature are associated with germline mutations in chromosome 22q11.2 and inactivation of these proteins.[11] Many of these did not have genetic studies performed on the tumour and some are reported in adults. This is related to the finding that most, if not all, MRT's of children harbour 22q deletions while adults with rhabdoid tumours rarely do.[10]

Making the correct diagnosis of MRT is important in terms of clinical implications. Patients with MRT of the liver have a reported mean survival of only 15 weeks,[3] while those with hepatoblastoma may be as high as 89% at 5 years.[12] Frequently, even after resection and chemotherapy, the disease will recur. A summary review including the case presented demonstrates the clinical behaviour and characteristics of these tumours [Table 1].

In this case, our 7-month-old patient presented with a heterogeneous right hepatic mass, elevated AFP (197 ng/mL), and mildly elevated AST and ALT. These findings are suspicious for hepatoblastoma, but AFP is usually much higher than that. The elevated AFP is more likely related to liver regeneration in this case. Histology showed polygonal rhadboid cells with prominent nucleoli and intracytoplasmic eosinophilic inclusions, features not typical of hepatoblastoma.

Hepatoblastoma of small cell undifferentiated histology can mimic MRT but do not have INI1 mutations.[13,14] Lack of reactivity with INI1 immunohistochemistry proved our patient's tumour to be a MRT of the liver. Similar to our patient, Nassan *et al*.[9] report a case of a 10-month-old male who developed pulmonary metastases while undergoing chemotherapy.

It is, therefore, important to keep MRT's in the differential of any primary hepatic tumour in a child. INI1 immunohistochemistry is an invaluable tool and should be employed in any suspicious scenario. Treatment and prognosis remain markedly different if MRT of the liver is diagnosed.

In summary, based on our index case and the review of literature [Table 1] we generated the following conclusions about primary MRT's of the liver. The average age of patients at diagnosis is about 2 years [26.4 months (range: 0-324 months)] with a similar gender distribution (15 female; 17 male). Seventy-one percent (23/32) of patients developed metastatic disease and the most common site for metastasis was lung. AFP was elevated above standard adult reference ranges in 36% (8/22) of patients with reported values. In children, however, AFP reference ranges are much higher than adults.[5] INI1 was negative in every case where the status was known (11/11). Five patients were living at last reported follow-up. The remaining 31 patients died of their disease or complications thereof. No standardized therapy regimen was utilized and disease progression did not appear to be related to therapy or age at diagnosis. There is no standardized reporting of survival in the literature as some authors use survival from diagnosis, others use survival post-therapy, a few mention no timeline, and one is not reported at all. To combat this we excluded from prognosis those cases that were not explicit (patients 6, 8, 14, 15, 17, 18, 20, 25, and 27), those reported as post-therapy (patients 16 and 21), and those still alive at last report (patients 10, 23, 26, 32, and 36). The remaining 20 cases suggest an average survival from diagnosis of approximately five and a half months (21 weeks) with a mortality rate of 86%. The survival time was slightly longer than that previously reported in the literature and suggests that overall survival is improving.[3,4]

As more cases are reported perhaps we will learn more about this entity, its behaviour, and develop better therapeutic approaches. Until then, MRT of the liver remains rare and difficult to cure.

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