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# Primitive Neuroectodermal Tumor of the Liver: A Case Report

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Ewing sarcoma/primitive neuroectodermal tumor is a rare tumor of soft tissues of thoracopulmonary regions, pelvis and lower extremities. Involvement of visceral organs by primitive neuroectodermal tumor is even rarer, with the kidney being the most commonly involved organ. Involvement of the liver has been reported in the form of metastasis from other primary sources presenting as liver abscess. We report a 20-year-old lady presenting with massive hepatomegaly, with computed tomography scan evidence of diffuse hepatomegaly and a normal porta and intrahepatic biliary radicles. She subsequently underwent ultrasonography-guided true-cut needle biopsy of the liver. Histopathology of the liver revealed nests of small round blue tumor cells in the background of hepatocytes infiltrating the liver, which expressed Mic-2 and Fli-1, and were negative for cytokeratin, desmin, hepatocyte-specific antigen (OCHIE5), synaptophysin, chromogranin A and CD-20. Immunohistochemistry revealed CD-99-positive. Extensive search regarding any possible different site of involvement by the tumor was negative. The patient responded to a combination therapy of vincristine, adriamycin and cyclophosphamide alternating with ifosfamide and etoposide 3 weekly over 43 weeks and has been doing well even after 1 year of diagnosis. The clinical presentation, the macroscopic aspect, together with the histological pattern, the cytological characteristic and the cellular immunophenotype lead to the diagnosis of primary primitive neuroectodermal tumor of the liver which responded well to combination chemotherapy.

*Key words: primitive neuroectodermal tumor – liver*

## INTRODUCTION

The peripheral primitive neuroectodermal tumor (PNET), first recognized by Arthur Purdy Stout in 1918, is a member of the family of 'small round-cell tumors' (1). Most of these tumors are diagnosed before the age of 35 years with a slight male preponderance, and primarily involve the central nervous system (CNS) (2). Although PNETs can occur in numerous solid organs such as the kidney, ovary, vagina, testis, uterus, cervix uteri, urinary bladder, parotid gland, heart, lung, rectum, pancreas and gall bladder, it is an extremely rare tumor entity (3). The liver involvement is uncommon and is usually in the form of metastasis from other primary source presenting as liver abscess (4). Primary PNET of the liver has never been reported to our knowledge.

## CASE REPORT

A 20-year-old girl presented with progressive distension of her upper abdomen, noticed by her mother for the first time 20 days prior admission, with a dragging sensation and heaviness in the same region for 15 days. She had no other complaints and her past history was unremarkable. Examination revealed the presence of pallor, huge hepatomegaly (liver span 28 cm) and a just palpable spleen. The liver was firm, smooth surface, sharp border and non-tender on palpation (Fig. 1). Significant findings in laboratory investigations included the presence of hypochromic microcytic anemia (hemoglobin 9.4 g/dl; normal range 11.5–15 g/dl) with anisopoikilocytosis, elliptocytosis and occasional polychromatic macrocytes, raised erythrocytic sedimentation rate of 58 at

the end of first hour, normal serum albumin (3.9 g/dl; normal range 3.8–5.3 g/dl), a slightly raised globulin (4.4 mg/dl; normal range 2.3–3.5 g/dl) and INR of 1.1. Liver enzymes were slightly raised (SGOT 58 IU/l; normal range 10–40 IU/l, SGPT 52 IU/l; normal range 10–40 IU/l). Alkaline phosphate was also slightly elevated (274 IU/l; normal range 110–230 IU/l). Serum lactate dehydrogenase was 200 IU/l (normal range 110–230 IU/l). Serum urea and creatinine were also normal and so was urine microscopy. Serum tumor markers, including $\alpha$-fetoprotein, carcinoembryonic antigen and CA 19-9, were negative. Ultrasonography (USG) and computed tomography (CT) scan of the abdomen showed an enlarged liver with normal intrahepatic biliary radicles and normal porta hepatis and mildly bulky kidneys with retained cortico-medullary differentiation (Fig. 2). Using a standard technique, under local anesthesia, she underwent USG-guided liver biopsy, using an 8 F true-cut needle. On microscopic examination (Figs 3–6), it reported a small round blue cell tumor (SRBCT). Nests of medium-sized round or oval tumor cells with enlarged round or oval nuclei with few mitotic figures and scant cytoplasm were seen in the background of hepatocytes. On immunohistochemistry, tumor cells expressed Mic-2 and Fli-1, and were negative for cytokeratin, desmin, hepatocyte-specific antigen (OCHIE5), synaptophysin and chromogranin A and CD-20. Immunohistochemistry revealed a strong expression of CD-99 (Figs 7 and 8).

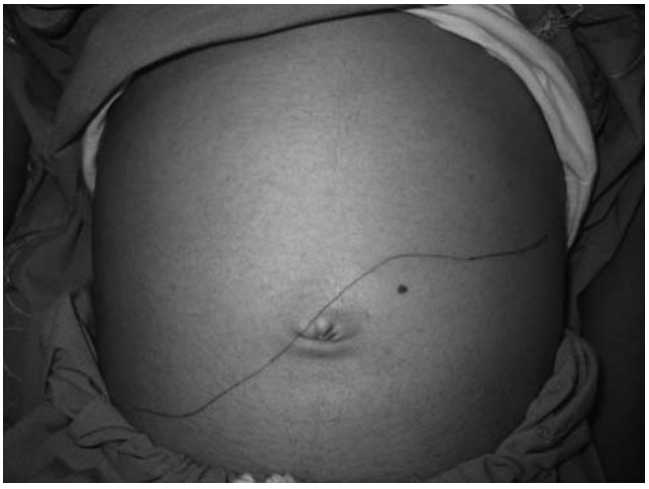

**Figure 1.** Hugely distended abdomen with surface marking of the enlarged liver. A color version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

A search for any other site of involvement by the tumor using CT scan chest, MRI of brain, whole body bone scan yielded negative results. Bone marrow aspiration showed normal cellularity with normal myeloid to erythroid ratio. On Prussian blue staining, there was evidence of decreased stainable iron. Biopsy was done from the left kidney and on microscopic study shows seven glomeruli with normal architecture.

Twenty-two days after admission, she received the first cycle of chemotherapy (VAC; vincristine 2 mg/m$^2$, adriamycin 75 mg/m$^2$ and cyclophosphamide 1200 mg/m$^2$). All the three drugs were given in a single day. VAC was alternated with IE [ifosfamide (1800 mg/m$^2$/day) given along with mesna over 5 days with etoposide (100 mg/m$^2$/day) given over the same 5 days] and the cycles were given every 3 weekly. The VAC/IE regimen used was adapted from the regimens used at Memorial Sloan Kettering Hospital and Dana–Farber Cancer Institute and Children's Hospital Boston for treating Ewing's family of tumors (5,6). Following the third cycle of VAC, she developed febrile neutropenia. She received two doses of G-CSF (Neupogen®) along with broad-spectrum antibiotics. She recovered; however, the subsequent cycle was delayed by 17 days. In subsequent cycles, she received adriamycin at 60 mg/m$^2$ and cyclophosphamide at 960 mg/m$^2$. In total, she received six cycles each of VAC and IE over a period of 43 weeks. Blood component transfusions were given as and when required.

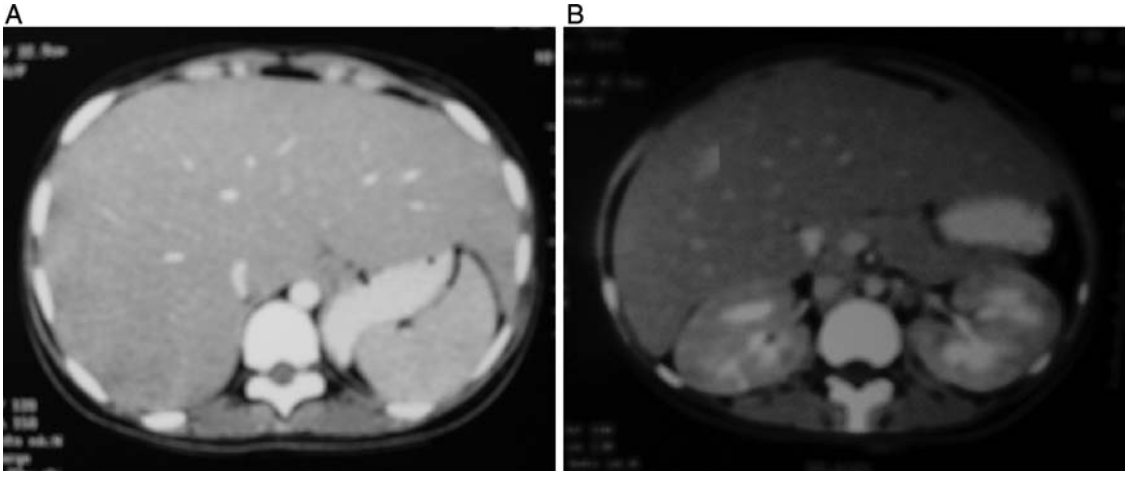


**Figure 2.** Images of computed tomography scan abdomen showing an enlarged liver with normal intrahepatic biliary radicles with bulky kidneys.

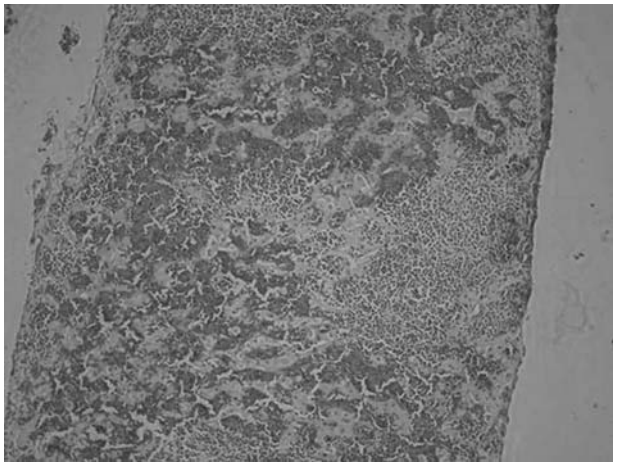

**Figure 3.** Low magnification showing section of the liver infiltrated by cells. A color version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

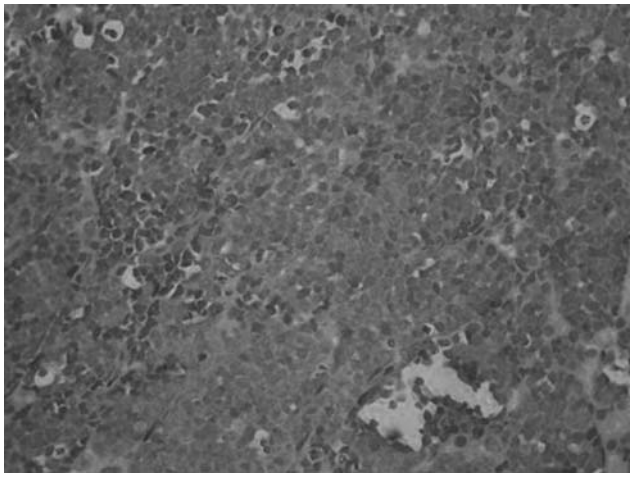

**Figure 4.** Higher magnification of the liver section showing infiltration by small round blue tumor cells.

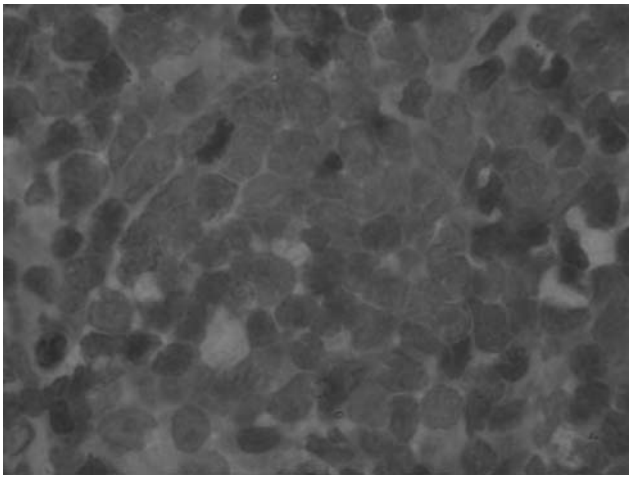

**Figure 5.** A further higher magnification of the liver section showing infiltration by small round blue tumor cells with few of the cells showing mitotic figures.

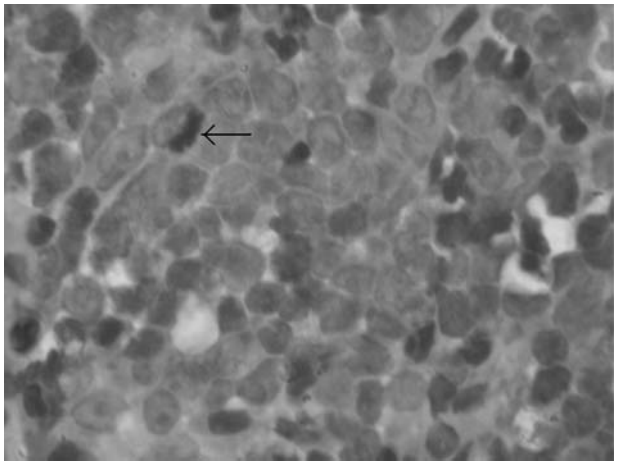

**Figure 6.** High magnification of liver section showing tumor cells. Arrow indicates mitotic figures. A color version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

Reduction in the liver size was observed as early as after the second cycle of VAC and continued throughout the therapy. At the end of 43 weeks, she was asymptomatic with liver palpable 2 cm below the costal margin and a nearly normal span. The liver chemistries had become normal. However, a repeat liver biopsy was not done, as the patient refused to give consent. The liver is an organ with low radiotolerance and radiotherapy of the liver is associated with significant side effects like acute radiation hepatitis. Further radiotherapy has a poor role in gross disease of solid tumors of the liver. Hence, the patient was followed up in the Liver Clinic of Medical College and Hospitals, Kolkata. The patient underwent detailed clinical examination during each visit of follow-up and any increase in the liver size during clinical examination and USG was looked for. Routine investigation and liver chemistries were repeated during each visit. It was planned to repeat CT scan in the case of any clinical deterioration. Last evaluated, she was doing well even after 1 year of diagnosis.

## DISCUSSION

PNET is a rare neural crest tumor classified on the basis of the site of origin into CNS PNET and peripheral PNET. PNET belongs to the 'SRBCT' family. Peripheral PNET occurs outside the CNS and has considerable overlap with Ewing's sarcoma, both sharing a common and unique translocation [t(11;22)(q24q12): fusion gene designated EWS/FLI-1]. PNET constitutes ~1% of all sarcomas (3).

PNET outside the CNS is mostly found within the deep soft tissue of the extremities and the paravertebral areas. The kidney is the most common visceral organ involved by PNET (7–9). Involvement of the liver has been reported in the form of metastasis from other primary sources presenting

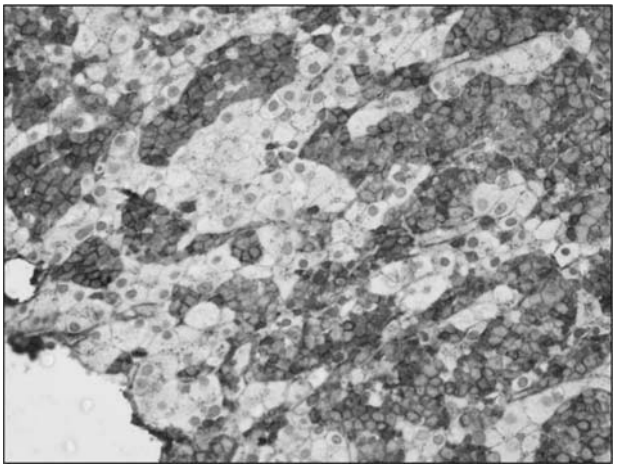

**Figure 7.** Immunohistochemistry of the liver section showing strong positivity for CD-99. A color version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

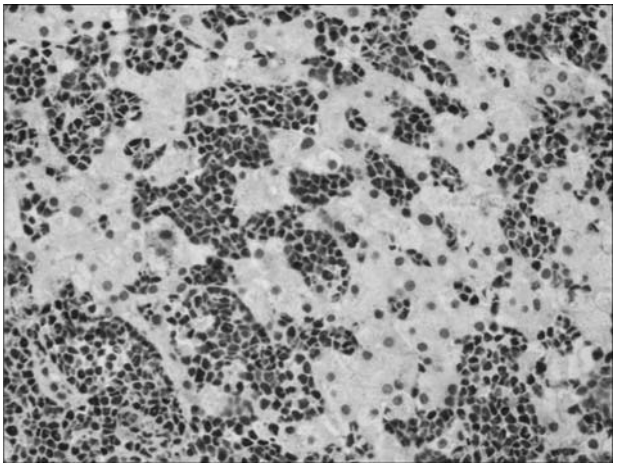

**Figure 8.** The liver section showing positivity for Fli-1 on immunohistochemistry. A color version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

as liver abscess. However, primary visceral PNETs are extremely rare and two cases of the small intestine and hepatic duct involvement, respectively, have been reported in children (7–11). To the best of our knowledge, this is the first case to be reported of PNET primarily involving the liver. The involvement of the liver in this case was in the form of diffuse infiltration.

Once PNET is diagnosed, the standard treatment is a systemic multi-agent chemotherapy combined with surgery and/or radiotherapy. Tumor dissemination at the time of diagnosis is associated with a poorer outcome compared with localized disease (12). A high initial complete response of 94% was observed in patients of PNET treated with VAC chemotherapy plus local radiation therapy (13). The best responses were reported with combinations based on anthracyclines (doxorubicin) and high doses of alkylating agents (cyclophosphamide or ifosfamide) (14). The most frequently used combination protocols include vincristine, actinomycin D, cyclophosphamide, doxorubicin and ifosfamide.

Our patient had diffuse involvement of the entire liver without objective evidence of involvement of any other organ. Resection of the liver was not an option here and she responded well to a combination therapy of VAC alternating with IE every 3 weekly over a period of 43 weeks. Radiotherapy was not considered to be necessary in her case.

Survival in PNET depends on multiple factors, one of the important being the degree of dissemination of disease, and various studies have shown a 5-year survival of 58–61% (14,15) with a median survival of 120 months (15). Our patient in this report responded well to chemotherapy alone and is asymptomatic and doing well even after 1 year of diagnosis. Isolated liver involvement was probably one of the factors responsible for good response to therapy and survival in her case.

To conclude, it may be said that PNET of primarily the liver is an extremely rare tumor and this is perhaps the first reported case. It was observed in a young lady with a subacute clinical presentation of upper abdominal swelling who responded well to combination chemotherapy. Although uncommon, PNET has to be considered in the differential diagnosis of atypical hepatic tumors in young patients.

## Conflict of interest statement

None declared.

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