Case Reports

Interpretation of Serum Alpha-Feto Protein in an Infant With Hepatomegaly

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In an oncological setting, the commonest causes of hepatomegaly in infancy are hepatoblastoma, neuroblastoma and vascular tumors (hemangiomas/ hemangio-endotheliomas)(l). They often present as asymptomatic liver enlargement. Hence the diagnosis rests on imaging and associated laboratory investigations which need confirmation by histology. Serum alpha-feto protein (AFP) levels often help exclude or confirm a diagnosis of hepatoblastoma. During infancy serum AFP levels have to be interpreted with caution as they remain relatively increased for the first few months after birth (2-4). We report here a 3 ½ month old infant with hepatomegaly, anemia and serum AFP of 700 ng/ ml who posed a diagnostic dilemma.

Case Report

A 3 ½ month (107 days) old male infant was referred to the Tata Memorial Hospital with gradually increasing hepatomegaly since birth, anemia and a four day history of constipation and urinary frequency. On examination, he was a pale, 8 kg infant with a firm, non-tender hepatomegaly, extending 6.5 cm below the costal margin and spanning 11.5 cm. The liver was smooth, regular and no bruit was audible over it. There were no signs of congestive cardiac failure.

Investigations revealed Hb of 5.6 g/dl (PCV=18%), total leucocyte count = 9.3 x 10^9/L; normal liver, kidney function tests, urinary VMA and X-ray chest. Serum AFP was 700 ng/ml. CT scan of the abdomen revealed multiple, well defined, low attenuation areas in both lobes of liver with post contrast enhancement *(Fig. 1);* sonogram, however was not helpful. CT guided FNAC done twice was reported as malignant round cell tumor. The aspirates were hemorrhagic on both occasions.

Initially a diagnosis of hepatoblastoma versus neuroblastoma was entertained. In view of the age at presentation, multifocal, single organ involvement, inadequately raised serum AFP and the child apparently thriving well for this volume of disease, the diagnosis of hepatoblastoma was considered unlikely. The presence of significant anemia and contrast enhancement on CT scan definitely raised the possibility of a vascular tumor. However, in the light of FNAC findings of round cell tumor, the child was labeled as neuroblastoma Stage IVS (unknown primary). He was put on the Neuroblastoma Infant Protocol which comprises of oral cyclophosphamide 150 mg/m^2 daily for 7 days followed by

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adriamycin 35 mg/m^2 IV on day 8. The cycle is repeated 3 weekly for 6 cycles.

When the child was brought for evaluation on Day 8 of his first cycle, a few reddish-purple cutaneous lesions were noted at the angle of the mouth (right side). Cutaneous deposits of neuroblastoma Stage IV S or a hemangioma were the logical possibilities and the lesion was biopsied. It proved to be a hemangioma. The association of hepatomegaly, integumentary hemangioma and congestive cardiac failure is classically described in vascular liver tumors although the present case had only two of these(5). As the pressure symptoms in the infant had been relieved with oral cyclophosphamide it was decided to withhold further chemotherapy and opt for an open biopsy of the liver, to confirm the correct histologic diagnosis. Histologically, the biopsy was reported as hepatic hemangioendothelioma. In view of the good response to cyclophosphamide, two more courses were given, cumulative cyclophosphamide dose of 35 mg/kg, equivalent to recommended dose (6,7). The liver regressed from 6.5 cm to 3.5 cm below costal margin (liver span 8 cm), serum AFP came down from 700 ng/dl, hemoglobin stabilized at 11.5 g/dl and CT scan showed good regression *(Figs. 1 & 2).* The child was on monthly follow up till thirteen

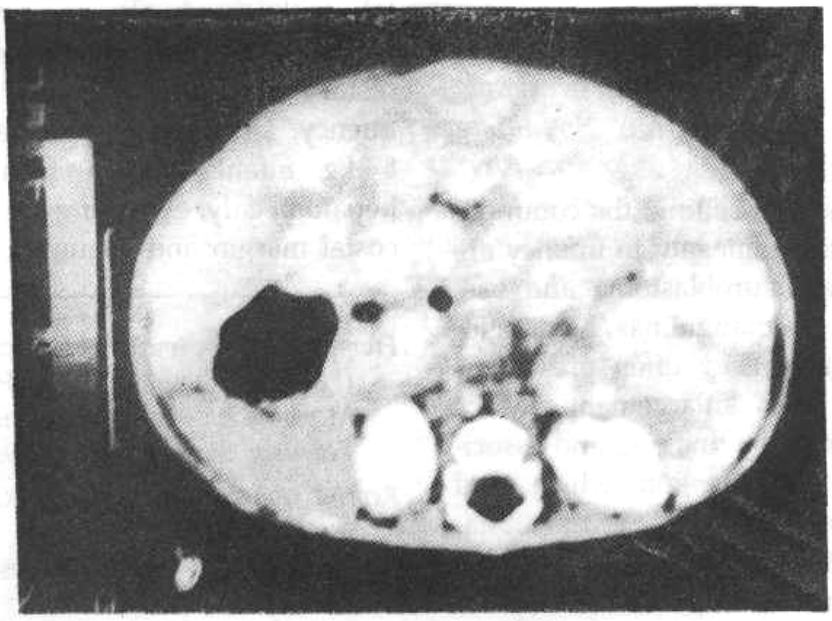

Fig. 1. Pre-treatment CT scan of abdomen.

months of age and is being followed at 3 monthly intervals subsequently. He is at present 16 months old and maintaining his growth curve.

Discussion

The authors are reporting this case not only because it is unusual and posed a diagnostic dilemma, but also to high-light a common error of wrong interpretation of alpha-feto protein levels during infancy.

Alpha feto protein, a glyco protein of 70,000 molecular weight, measured by specific radioimmunoassay is produced almost exclusively in the fetal liver and yolk sac. Synthesis almost completely ceases at birth and it disappears from serum with an average life of 3.5 days during the first week of life (2-4). From levels of 1,00,000 ng/ml at birth it reaches near adult values of (<10 ng/ml) by 10 months of age(2-4).Hence it remains at relatively high levels during early infancy and normograms are recommended for interpretation in infancy.

AFP may, however, reappear in sera of patients suffering from hepatoblastoma (levels usually >50,000ng/ml), hepatocellular carcinoma and yolk sac tumors(4). The levels in these conditions are usually very high. Small elevations in serum AFP are also known to occur in inflammatory (hepatitis) and neoplastic *(i.e.,* neuroblastoma, hemangioma in infancy) conditions of the liver(2,6). In the present case, there was a marginal elevation of serum AFP (700 ng/ml) as against an expected value of 15-300 ng/ml, which may well occur in hemangioendotheliomas of the liver(5,8).

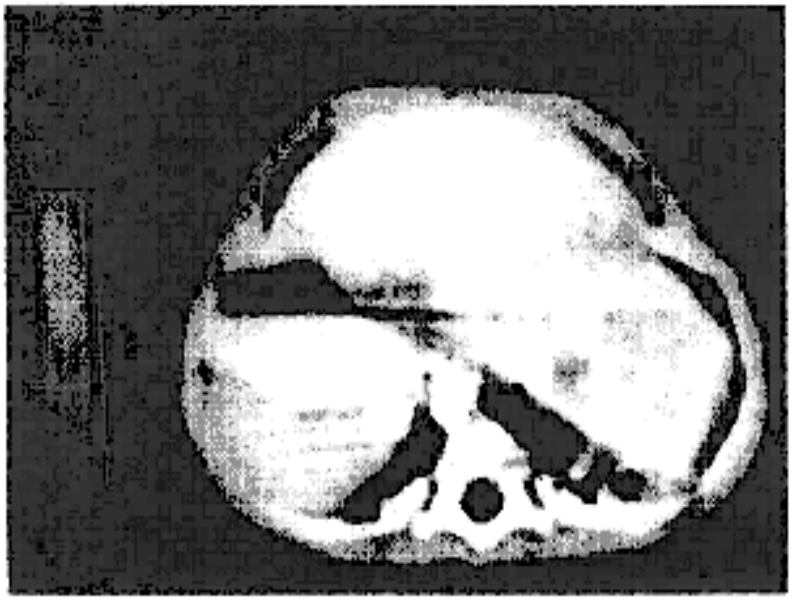

Fig. 2 Post-treatment CT scan of abdomen.

The interpretation of the FNAC always has limitations (9,10). It involves interpretation of scattered cells, without the benefit of exact architectural details. The two aspirates in these cases drew small deeply staining oval round cells in an intensely hemorrhagic background. The logical conclusion in FNAC of the child with hepatomegaly seemed to be a malignant round cell tumor which was largely undifferentiated. Co-relation with the histology revealed that the cells were part of the vascular tumor and not blastemal in nature.

Once the diagnosis of hemangioendothelioma was established, the question was whether or not to treat the child. Although 90-95% of vascular tumors of the liver remain small and asymptomatic, it is the large, symptomatic ones that account for the complication associated mortality of 80% (5). Of the various modalities of treatment available, hepatic artery embolization, hepatic artery ligation and surgical excision are usually reserved for solitary or localized lesions (5,7). Radiotherapy has also proved to be successful in selected cases (5-7). It is best avoided in infants because of its long-term sequelae. Medical management includes steroids and cyclophosphamide. Steroids are usually the first line of management, 30% of cases showing remarkable response (ll). It may be used alone or with one of the other modalities. Cyclophosphamide in doses of 10 mg/kg/day for 3-4 days every month for three cycles has been reported to be effective (7). It is usually reserved for cases non-responsive to steroids and not suitable for surgical intervention. Long-term complications like second malignancy are unlikely in view of the short course and small dose of the drug required. In the reported case, as the child had shown a remarkable response to the initial course of cyclophosphmide (cumulative dose=35 mg/kg, equivalent to recommended dose), it was decided to continue with the same. He went on to receive two more cycles of the same followed by close follow up. He is maintaining his growth curve at 13 months of age.

In conclusion, we feel that ready reference to nomogram is mandatory to avoid fallacious interpretation of serum AFP, especially during early infancy.

REFERENCES

1. Rao BM, Green AA. Hepatic tumors in children and adolescents. Sci Pract Surg 1987, 8: 187-218.
2. Tsuchida Y, Endo Y, Saito S, Kaneko M, Shiraki K, Ohmi K. Evaluation of alpha-fetoprotein in early infancy. J Pediatr Surg 1978,13:155-156.
3. Gitlin D. Normal biology of alpha-fetoprotein. Ann New York Acad Sci 1975, 259: 7-16.
4. Tsuchida Y. Markers in childhood solid tumors. *In:* Pediatric Surgical Oncology. Ed. Hays DM Orlando, Grune and Stratton, 1986, pp 47-62.
5. Stevenson RJ. Abdominal masses. Surg Clin North Am 1985, 65:1481-1504.
6. Holcombe III GW, O'Neill JA Jr, Mahboubi S, Bishop HS. Experience with hepatic hemangioendothelioma in infancy and childhood. J Pediatr Surg 1988, 23: 661-666.
7. Stanley P, Geer GD, Miller JH, *et al.* Infantile hepatic hemangiomas: Clinical features, radiologic investigations and treatment of 20 patients. Cancer 1989, 64: 936-949.
8. Ramadwar RH, Deshmukh SS, Oak SN, Karmarkar SJ. Infantile hemangioendothelioma of the liver in the neonate. Indian Pediatr 1993, 30: 1441-1444.
9. Chinoy RH. Fine needle aspiration cytol ogy of lesions occupying the soft tissue compartment. *In:* Aspiration Cytology for Clinicians and Pathologists. Ed. Krishnarnurthy Bombay, Tata Memorial Center, 1991, pp 138-162.

10. Hajdu SI, Ehya H, Frable WJ, *et al.* The value and limitations of aspiration cytology in the diagnosis of primary tumors. A symposium. Acta Cytologica 1989, 33: 741-790.

11. Enjolras O, Riche MC, Merland JJ Escande JP. Management and alarming hemangiomas in infancy: A review of 25 cases. Pediatrics 1990,85:491-498.

ERRATUM

In the IAP Time Table published in Indian Pediatrics, Vol. 32, December 1995, p. 1329, Immunization Session (5) for OPV (5) and HB (3), the recommended age should read as 6-9 months instead of 6-9 weeks. The corrected version is reproduced below.

Immunization Session No.	Vaccine and dose			Recommended age
1.	BCG	OPV (1)	HB(1)	Birth to 2 weeks
2.	DPT (1)	OPV (2)	HB (2)	6 weeks
3.	DPT (2)	OPV (3)	..	10 weeks
4.	DPT (3)	OPV (4)	..	14 weeks
5.	..	OPV (5)	HB (3)	6-9 months
6.	Measles	..	..	9 months
7.	MMR	..	..	15-18 months
8.	DPT (B1)	OPV (6)	..	18-24 months
9.	DPT (B2)	OPV (7)	HB (B1)	5 years
10.	TT (B3)	..	..	10 years
11.	TT (B4)	..	HB (B2)	15-16 years