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A Clinico – Pathological Study of Metastatic Hepatic Lesions with Special Reference to Metastasis from Unusual Primary Sites

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Abstract:

Objective: *Liver is a potential site for blood borne metastasis for many malignancies of human body, besides giving rise to a primary tumor itself. Often, hepatic metastasis can be the only mode of presentation in certain tumors that prompt us to search for the primary sites. Our study aims at proving that other than gastrointestinal malignancies, specially adenocarcinoma of pancreas, stomach, large gut, gall bladder etc, which are generally known to be notorious for hepatic metastasis, liver can also be a site of metastasis for malignancies from a spectrum of very unusual primary sites. Also through our study we can establish FNAC as a simple, safe, quick and cost effective tool in diagnosing metastatic hepatic lesions.*

Materials & methods: *After doing USG guided FNAC in 94 patients, 57 cases were primarily diagnosed as metastatic hepatic lesions, of which 22 cases have a spectrum of unusual primary sites like adrenal, kidney, soft tissue, gastrointestinal & retroperitoneal sarcomas, ovary, skin & lung, while the other 35 cases were adenocarcinoma of gastrointestinal tract origin, confirmed later by histopathology examination of metastatic hepatic mass and resected primaries, as & when possible.*

Result: *Thus 22 out of 57 cases i.e. 38.5% of our cases of hepatic metastasis showed unusual primary sites, which cannot be ruled out as insignificant.*

Conclusion: *So, this study not only helps us to establish image guided FNAC as an easy, fast, safe & a firsthand tool to diagnose metastatic deposit in liver, but also reveals the fact that liver too can be a site of metastasis for malignancies, from unusual sites other than gastrointestinal tract.*

Keywords*: Guided FNAC; liver metastasis; unusual primary neoplasm*

I. Introduction

Liver is a major organ for metastasis of all types of malignancies in human body, other than being a site for primary tumor itself, in many cases. Often, liver metastasis provides an important clue in the diagnostic search of a primary lesion elsewhere in the body. Even, when the patient is unsuitable for surgical biopsy, only image guided fine needle aspiration cytology (FNAC) from the lesion, can turn out to be a simple way of directing clinician & pathologist to search for the unknown primary.

This hospital based study was thus undertaken to ascertain the cytological diagnosis of various metastatic hepatic lesions, with special reference to lesions from unusual primary sites, thus establishing the role of FNAC as a fast, easy & cost effective tool in detecting metastatic hepatic lesions. [1, 2]

II. Materials And Methods

The present study was conducted on 94 patients, presenting with symptoms like pain in upper abdomen, weight loss, fever, anorexia jaundice and palpable or non palpable right hypochondriac mass lesions (proved to be of hepatic origin by ultrasonography), attending various in-patient & out-patient departments of Burdwan Medical College & Hospital ,within a period of two years – August2009 to July 2011.

Both solitary & multiple nodular lesions were aspirated. Hemangioma and simple hepatic cysts were not included in this study. No age or sex limit was taken as criteria for selecting cases. Patient's coagulation profile was taken into account for safety purpose before the procedure. USG guided FNAC was done in all hepatic mass lesions, using a 22G spinocaine needle, attached to 20ml disposable syringe. The smears were stained by Papanicolaou, May-Grunwald-Giemsa (MGG), and Hematoxylene & Eosin stain (H&E). The specimen for histopathology were obtained(40/94 patients) by core needle biopsy which was performed using Vim-Silverman liver biopsy needle and microscopic examination was done after tissue processing and H&E staining of the tissue section.

III. Results

Among 94 cases, aspirate from 4 cases were inadequate for interpretation, so diagnostic yield was 97.8%. 26 cases(27.7%) were benign hepatic lesion, primary hepatic neoplasm were found in7 cases (7.4%) and rest 57 cases(60.6%) were categorized as metastatic hepatic lesions.

Distribution of 57 cases of metastatic hepatic lesions, 35cases (61.4%) turned out to be from usual primary sites like gall bladder, pancreas, small & large gut adenocarcinoma, which were confirmed eventually by histopathology examination of resected primaries. Other 22 cases (38.6%) however were tracked down to metastasize from unusual sites like kidney, adrenal, lung, ovary, retro peritoneum, skin, & gastrointestinal stromal tumor (GIST).

Non neoplastic and benign hepatic lesions included 14 cases (53.9%) of hepatic abscess (both pyogenic & amoebic), 5 cases(19.2%) of hydatid cysts, hepatic adenoma in 3 cases(11.5%) and cirrhosis & granulomatous hepatitis had two cases(7.7%) in each group. Most cases were in the age range of 20 to 30 years with male preponderance.

All the hepatocellular carcinomas were confirmed by cyto-histopathological examination supported by serum Alpha Feto Protein (AFP) estimation and study of viral markers (Hbs Ag and Anti HCV). Distribution of HCC showing male preponderance with age distribution ranges from 40years to60 years.

Observing the distribution of cases of hepatic metastasis, which was main focus of our study, showed adenocarcinoma of gastrointestinal tract had major sharing (61.4%), among which gall bladder was the most frequent site, followed by large gut 9 cases, stomach 7 cases, and pancreas had 1case. **[Table-1].**Majority of cases in this group of usual primaries of gastrointestinal tract origin showed male preponderance with most of the cases in the age group of 4th to5th decade**[Table-2].**

Considering the hepatic metastasis from unusual primary sites, adrenal neuroblastoma were most common, having 5 cases, and Malignant GIST, wilms'tumor and ovarian neoplasm shares 3 cases in each group. Renal cell carcinoma, uterine leiomyosarcoma and retroperitoneal sarcoma had 2 cases in each, and 1 case each of bronchogenic carcinoma and malignant melanoma of skin presented as a hepatic metastasis**. [Table-3]**Among those cases hepatic metastasis helps to drag the attention to diagnose the primaries like bronchogenic carcinoma and two cases of adrenal neuroblastoma, initially diagnosed as storage disorder by imaging modalities. Patient with past history of uterine leiomyosarcoma (TAH&BSO done 5years back) was presented with multiple cuteneous metastasis along with hepatic secondaries. These unusual primaries showed 12 cases in female and 10 cases in male with majority of cases in age group of >49 years.

Regarding hepatic abscess, pyogenic abscess showed predominance of neutrophils in the necrotic background and trophozoites of Entamoeba histolytica were found in cases of amoebic hepatic abscess. Refractile hooklets in a background of inflammatory cells and degenerated hepatocytes were found in cases of hydatid cyst of liver.

Hepatocellular carcinoma was distinguished from metastatic lesions in cytology smear having following features of broad trabeculae with endothelial rimming or transgression of vessels in the cell clusters, bare nuclei with anisonucleosis in the background, large pleomorphic polygonal cells with eosinophilic granular cytoplasam, central nucleus with prominent macro nucleoli and intracytoplasmic bile pigments and multinucleated giant cells with atypical nuclei. However poorly differentiated cases required additional support like viral markers, serum AFP and final confirmation by histopathology examination.

Metastatic adenocarcinoma shows columnar to cuboidal cells arranged in acinar pattern or pallisaded arrangements. The individual cells are having nuclear pleomorphism and atypia by virtue of karyomegaly with increased N:C ratio, hyperchromasia and prominent nucleoli. Background shows normal hepatocytes.

Aspirates of gastrointestinal stromal tumors demonstrate relatively monomorphic and uniform spindle cells in loose aggregates and singly whereas cells of leiomyosarcoma shows more pleomorphism and less vascularity. Metastatic RCC shows polygonal cells arranged singly and in clusters. The nuclei are round with prominent nucleoli, and the cytoplasm is clear or granular. Metastatic squamous cell carcinoma cytology smear demonstrate polygonal or spindled cells arranged singly or clusters having hyperchromatic nuclei with irregular outline along with dense, nonvacuolated cytoplasm with necrotic background. Metastatic melanoma smear dominated by dispersed cells with plasmacytoid appearance, having eccentrically located hyperchromatic nuclei, prominent nucleoli and intranuclear inclusion. Metastatic wilms' tumor and neuroblastoma recapitulate its cytological features same as its primary.

IV. Discussion

USG guided FNAC of hepatic mass lesion plays an important role in diagnosis of various benign and malignant lesions with minimal intervention and little risk of complication. On the other hand effective cytological diagnosis helps to reduce more complicated and invasive procedures for correct diagnosis of hepatic lesions.

In this present study, diagnostic yield was 95.75%. 83.4% diagnostic yield was obtained by Rasnia A et al in their study and similar result were observed by Hemalatha AL et al.[3,4]

FNAC findings of metastatic lesions correlated 100% with both the cytological diagnosis of primaries as well as histopathological diagnosis of resected primary tumors as and when possible but one case of cirrhosis and hepatic abscess diagnosed by cytology was actually hepatocellular carcinoma confirmed by histopathology.

In this study malignant hepatic lesions outnumbered the benign lesion, similar results were obtained by **Rasania A et al** in their study which account 23.3% cases were benign and 67.7% were malignant[3]. **Farinati F et al** also found 27% benign hepatic lesion and 73% cases were malignant.[5] Among the malignant hepatic lesions majority of cases were metastatic in origin followed by hepatocellular carcinoma, similar results were obtained by Khanna et al and Nosher et al.[6,7] But Hemalatha AL et al found 44.4% cases of HCC as compared to metastatic hepatic lesion in 27.7%.[4] Equal number of cases of HCC and metastatic lesion was observed by Ahuja A et al.[8]

HCC cases showed male preponderance and similar result was also observed by Ahuja A et al and Mallikarjuna Swamy et al.[8,9] In present study HCC cases were distributed in age range of 40 to 60 years where as age range of HCC in study of Ahuja A et al was from 35 to 82 years. [8]

5/7 cases of HCC had solitary space occupying lesion and 2 cases had multiple hepatic lesions. Ahuja A et al found solitary SOL in 17/25cases in their study.[8] In present study 57.1% (4/7) cases show elevated serum AFP level and HBsAg and anti HCV was positive in 71.4% (5/7) and28.6% (2/7) cases respectively. **S.O.Ola et al in their** study found 64% patients of HCC had elevated serum AFP level and HBsAg and Anti HCV was positive in 71.4% and 14.3% of HCC cases respectively [10].

In our study of metastatic hepatic lesions most of the cases primary lesion was identified except in three cases where primary lesion was not detected but in the study of Nosher et al primary site of origin was not detected in majority of hepatic metastasis.[7]

Our study showed an overall male preponderance of **52.6% (20 cases)** in case of metastatic lesions from usual gastro intestinal tract adenocarcinoma, whereas a slight female preponderance of **54.5%(12 cases)** , in case of metastasis from unusual primary sites.

Metastasis from usual gastrointestinal adenocarcinomas had a higher incidence in elderly age group **74.2%** in age group of >49 yrs., whereas unusual tumors had less incidence of metastasis in liver at similar age group people- **45.4%** ,but still majority of the cases were belong to in this age group.

Another interesting finding was that in the pediatric age group of **0-15 years**, neuroblastoma & wilms'tumor were the major malignancies metastasizing to the liver, among which neuroblastoma showed higher percentage of incidence (**62.5%**) & a male preponderance.

However, 22 (38.6%) out of total 57 cases showed a spectrum of unusual primary sites, other than gastrointestinal tract. 5 cases(22.7%) were found to be metastasis from adrenal neuroblastoma, 3cases (13.6%) each were metastasis from GIST, wilms'tumor and ovarian neoplasm, followed by 2 cases(9.1%) of metastatic deposit from uterine leiomyosarcoma, Renal cell carcinoma, and retroperitoneal sarcoma in each group with 1 case(4.5%) each as deposit from bronchogenic carcinoma and malignant melanoma of skin presented as unusual primary site. Kuo et al found 0.9%,0.4% and 0.1% cases of squamous cell carcinoma, sarcoma and melanoma respectively.[11] Shak K et al also reported that squamous cell carcinoma, renal cell carcinoma and malignant melanoma was the infrequent cause of hepatic metastasis.[12] Regarding metastatic hepatic sarcomas, leiomyosarcomas and GIST are most commonly encountered. But identification of primary, cyto-histopathological correlation and immunohistochemistry is the ultimate pathway for confirmation of diagnosis in most of these cases. Thus, metastasis from unusual primary sites account for 22cases (**38.6%)** out of 57 cases in our study which could not be ruled out as an insignificant proportion.

V. Conclusion

The most important aspect that came in forefront after our study is the role of USG guided FNAC as a safe, time saving, cost effective procedure in diagnosing as well as detecting the exact nature of metastatic hepatic lesions.Though adenocarcinomas from different portions of digestive tract are notorious for liver metastasis, this study proves that, malignancies from a spectrum of other unusual sites like neuroblastoma, kidney tumors like wilms'tumor & renal cell carcinoma, ovarian epithelial tumors, retroperitoneal sarcoma, gastro intestinal stromal tumor(GIST) ,have a significant potential for hepatic metastasis, as well.Often when, primary tumors are not detectable on the first hand, or not classifiable, cyto diagnosis of liver metastasis helps to detect the lesion, like as in a case of bronchogenic carcinoma (squamous cell variant).Detection of liver metastasis, however can also helps us to mark the malignancy as high grade & in advanced stage, thus helping in pursuing proper treatment. At last, it should be mentioned that a close collaboration between clinician, radiologist & pathologist must be maintained to potentiate the diagnostic accuracy of hepatic metastatic lesions & increase the survival of the patients.

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Table-1: Distribution of cases of metastatic hepatic lesions from usual primary sites like gastrointestinal tract

Primary sites	Number of cases	Metastatic presentation	Cytological diagnosis	Histopathological diagnosis
Gall bladder adenocarcinoma	**15**	7 cases-solitary nodules. 8cases-multiple nodules.	11 cases- adenocarcinoma. 4 cases- signet ring variant of adenocarcinoma.	10 cases- adenocarcinoma. 5 cases- not resected.
Stomach	**07**	Multiple hyperechoeic or hyperechoeic SOL showing targetoid appearance in USG.	Adenocarcinoma.	6cases-Adenocarcinoma 1 case- signet ring variant of adenocarcinoma.
Large gut	**09**	Multiple hyperechoeic or hypoechoeic SOL showing targetoid appearance in USG, with foci of calcification at places.	Adenocarcinoma.	Adenocarcinoma
Pancreas	**01**	Solitary, large lesion with central necrosis, mimicking primary hepatic malignancies.	Adenocarcinoma.	Adenocarcinoma
Unknown	**03**	Multiple hepatic lesions.	Adenocarcinoma.	Adenocarcinoma

Table-2: Age –sex distribution of metastatic hepatic lesion from usual primary sites

Sex	Number of cases	Age-0-15 yrs	Age-16-30yrs	Age-31-49yrs	Age>49yrs
Male	20	0	2	4	14
Female	15	0	1	2	12
Total	35	0	3	6	26

Table-3: Distribution of cases of hepatic metastasis from unusual primary sites (other than G.I.T)

Type of primary tumor	Number of cases	Presentation of the liver SOL.	Cytodiagnosis of hepatic SOL.	Histopathological diagnosis.
Gastrointestinal stromal tumor (GIST)	03	Presented as large solitary lesion mimicking primary hepatic SOL.	Sarcomatous lesion, probably GIST	GIST
Adrenal neuroblastoma	05	Presented as multiple small nodules involving both lobes of liver along with involvement of other organs.	3cases- diagnosed as neuroblastoma. 1 case as PNET.	3 cases confirmed histologically as neuroblastoma.
Kidney - Wilm's tumor	03	Multiple hepatic nodules of various sizes.	?PNET/?Wilm's	Wilm's tumor
Kidney- renal cell carcinoma	02	Solitary large lesion in right lobe of liver	Renal cell carcinoma	Renal cell carcinoma-clear cell variant.
Uterine leiomyosarcoma	02	Multiple hypoechoeic lesions in both lobes	Metastatic sarcomatous lesion.	Leiomyosarcoma
Ovary	03	Multiple hypo/hyperechoeic SOL with foci of calcification	Papillary adenocarcinoma	Serous papillary cystadenocarcinoma.
Bronchogenic carcinoma	01	Solitary nodule in right lobe	Squamous cell carcinoma	Squamous cell carcinoma.
Skin- malignant melanoma	01	Multiple hepatic nodules with some showing central necrosis	?Melanoma	Malignant melanoma
Retroperitoneal sarcoma	02	Large solitary nodule in liver	Pleomorphic sarcoma	Resection not done.

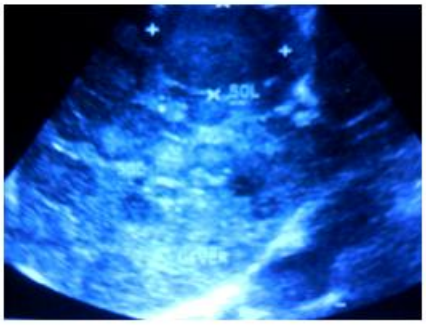

Figure-1: Ultrasonogram showing multiple hepatic nodules- a picture of metastasis

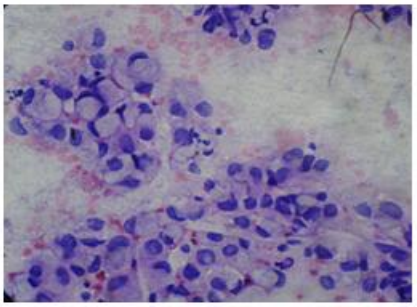

Figure-2: Guided FNAC from liver showing Signet ring cell adenocarcinoma of stomach. (H&E X 400)

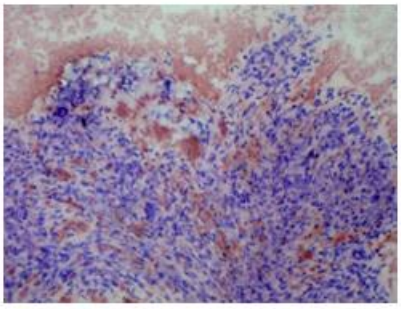

Figure-3: FNAC smear from liver shows sarcomatous lesion, GIST. (H&E X 100)

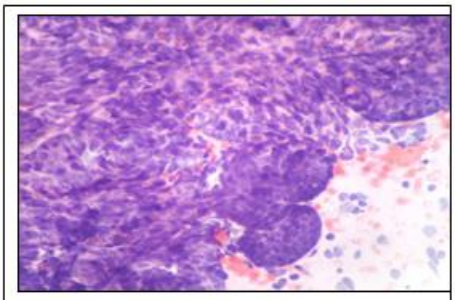

Figure-4: FNAC smears showing epithelial component with gland like arrangement of primitive cells in metastatic Wilms'tumor. (H&Ex400)

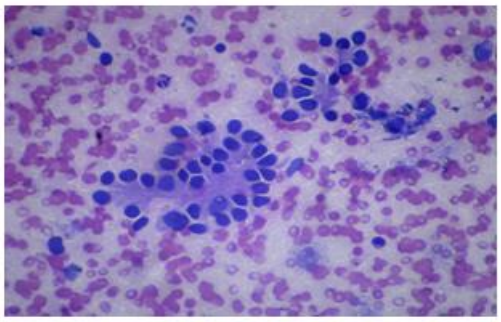

Figure-5: High power view (40X); H&E showing rosette with central neuropil in neuroblastoma. (H&Ex 400)