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The value of fine needle aspiration biopsy in the diagnosis of metastatic liver tumours

Karaciğerin metastatik tümörlerinin tanısında ince iğne aspirasyon biyopsisinin değeri

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Background/aims: *Fine needle aspiration biopsy is a useful tool in the diagnosis of primary malignancies and metastatic lesions of the liver. The aim of this study was to determine the types and features of tumors diagnosed by this method and the difficuities in differential diagnosis.* ***Methods:*** *Fine needle aspiration biopsy smears from 704 patients with metastatic liver lesions were reviewed.* ***Results:*** *Among the metastastatic carcinomas in which their primary origin was identified, pulmonary carcinomas were the largest group. While colon adenocarcinoma was most prevalent (21.65%) where the primary origin of metastatic tumors was identified, followed by breast carcinoma (20.10%) and gastric adenocarcinoma (19.59%). The cases which cannot be differentiated from hepatocellular carcinoma in cytologic examination are invasive ductal carcinoma, renal cell carcinoma and squamous cell carcinoma.* ***Conclusions:*** *Pulmonary and colon carcinomas are the common metastatic tumors of the liver.*

Key words: Fine needle aspiration biopsy, metastatic lesion, hepatocellular carcinoma.

Amaç: *İnce iğne aspirasyon biyopsisi karaciğerde primer maligniteler ile metastatik lezyonları ayırmada yararlı bir yöntemdir.* ***Yöntem:*** *Metastatik lezyonu olan 704 hastadan alınan karaciğer ince iğne aspirasyon biyopsisi si yeniden değerlendirildi.* ***Bulgular:*** *Primer odağı bulunan karsinomlar içinde en geniş grubu akciğer kanserleri oluşturmaktadır. Primer odağı bulunan adenokarsinomların en çoğu % 21.65 ile kolon adenokarsinomudur. Bunu % 20.10 ile meme ve %19.59 ile mide adenokarsinomları izlemektedir. Sitolojik incelemede hepatosellüler karsinom ile en çok karışan tümörler invaziv duktal karsinom, renal hücreli karsinom ve yassı hücreli karsinom olarak sıralanmaktadır.* ***Sonuç:*** *Pulmoner ve kolon kanserleri karaciğerin en sık metastatik tümörleridir.*

Anahtar kelimeler: İnce iğne aspirasyon biyopsisi, metastatik lezyon, hepatosellüler karsinom.

INTRODUCTION

Fine needle aspiration biopsy (FNAB), guided by modern imaging techniques, has become increasingly important in the diagnosis of hepatic malignancies. When assessed with laboratory results and findings of physical examination, cytological examination provides useful information for diagnosis (1-12), with FNAB allowing early detection of hepatocellular carcinoma (HCC) and differentiation of primary and metastatic tumors (1). In addition, it is one of the cheapest and the least time consuming techniques aiding diagnosis of any lesion in the liver suspected of being malignant (1-12).

There have been many studies to determine the cytological features of HCC. In all series, atypical cells of this carcinoma have been reported to have a nucleus located in the cell center and a well-defined, large polygonal cytoplasm (1,10,12-15). In addition, bile pigments and hyaline bodies can be helpful in diagnosis of the disease (12,16-18). Tumor cells show a trabecular sequence in HCC (1,14).

Metastatic liver tumors appear frequently. Cancer cells reach the liver via the portal vein, hepatic arteries and hilar lymphatics, or they directly invade the liver, which is a suitable environment for growth of tumor cells (19). In this study all cases of metastatic tumor diagnosed by FNAB were evaluated, the most frequent types of tumors and their cytological features determined

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Table 1. Cytological diagnoses of liver tumors on FNAB

Diagnosis	*n*	*%*
Benign Lesions	176	13.86
Primary Tumors	390	30.71
Metastatic Tumors	704	55.43
Total	1270	100

and the difficulties encountered in cytological differentiation of HCC from other tumors discussed.

MATERIALS AND METHODS

This study included 704 cases of liver tumor diagnosed by FNAB in the Department of Clinical Cytology of Ankara University between 1988 and 1998. Their cytological diagnoses were confirmed by review of archive records. General characteristics of the patients and clinical findings were obtained from the archive records of Ankara University and patient records of the Department of Clinical Cytology.

The FNAB was performed by a clinician under the guidance of computed tomography or ultrasonography. A 22 gauge needle, 90mm in length, was used for aspiration biopsy. Aspirated materials were spread on a slide (2-20mm), dried in air, then stained with May-Grünwald-Giemsa (MGG).

All materials were assessed by two cytopathologists blinded to the clinical diagnoses. All cases of malignancy, except for those of HCC, were classified according to cytological features and the similarities and differences between these malignancies and HCC were determined.

Table 3. Distribution of metastatic liver adenocarcinomas by their primary foci

Organ	*n*	*%*
Lungs	8	4.14
Stomach	38	19.59
Colon	42	21.65
Gallbladder	8	4.12
Pancreas	17	8.76
Breast	39	20.10
Ovaries	24	12.37
Prostate	6	3.09
Kidneys	6	3.09
Suprarenal Glands	6	3.09
Total	194	100

Table 2. Metastatic tumors of the liver

Diagnosis	*n*	*%*
Adenocarcinoma	443	62.93
Mucinous Adenocarcinoma	47	6.68
Malignant Epithelial Tumor	95	13.49
Squamous Cell Carcinoma	45	6.39
Small Cell Carcinoma	43	6.11
Malignant Melanoma	9	1.28
Lymphoma	12	1.70
Malignant Mesenchymal Tumor	10	1.42
Total	704	100

RESULTS

A total of 1270 patients underwent FNAB and the diagnosis of malignancy was confirmed by cytological examination between 1988 and 1998. Of these patients, 13.86%, had non-neoplastic lesions, 55.43% had metastatic tumors and 30.71% primary liver tumors (Table 1).

More than half of the patients had metastatic liver tumors (55.43%), forming the largest group in our series. Cytological diagnoses of these cases are shown in Table 2. There were 317 females and 398 males, with a mean age of 68 years. There were widespread signs of tumoral involvement such as pulmonary involvement with accompanying metastatic liver tumors, peritonitis carcinomatosa, lymphadenopathies and bone involvement in patients with adenocarcinoma (AC) in whom no primary tumor could be found and in patients in whom metastatic malignant tumor (MMT) was diagnosed, but types of the tumor could not be identified. Neither the biopsy specimens obtained from the liver and metastatic tumors nor the imaging techniques aided identification of the primary tumor. In addition, clinical findings, cytological examination and other diagnostic aids did not help determine whether the primary tumor originated from the gastrointestinal system or ovaries (especially in females) in cases of mucinous adenocarcinoma (MAC), which accounted for 6.68% of all malignancies.

Cases of adenocarcinoma, in which the primary tumor was detected and the organs from which they originated identified, are shown Table 3. The largest group was adenocarcinoma of the colon (21.65%), followed by breast carcinoma (20.10%) and gastric carcinoma (19.59%).

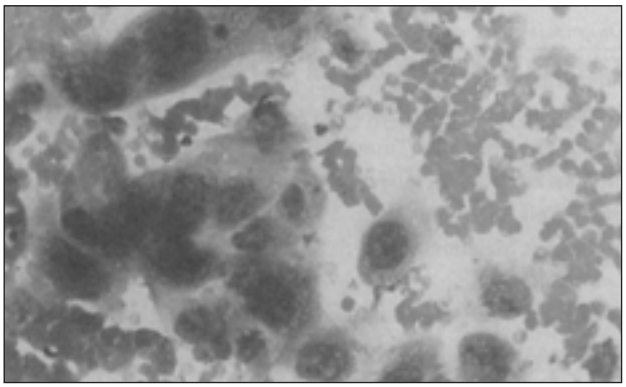

Figure 1. Atypical cells with a large cytoplasm and a centrally located nucleus in metastasis of stomach adenocarcinoma (x400;MGG)

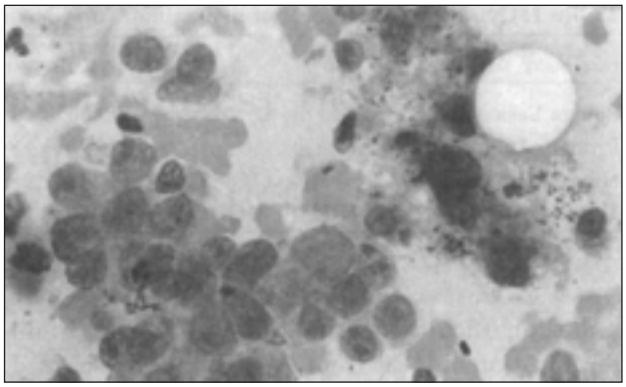

Figure 2. Metastasis of stomach adenocarcinoma and reactive hepatocytes at the bottom on the left

Pulmonary carcinoma had the highest rate of metastasis apart from adenocarcinoma, whose primary focus was determined. Half of the carcinomas originating from the lungs and metastasizing to the liver were squamous cell carcinomas (Table 4), with more than half of all squamous cell carcinomas in the liver (27 out of 45 cases) originating from the lungs. The remaining metastases were thought to stem from the gallbladder, pancreas and bile ducts, but the primary tumor could not be found. The primary tumor was located in the lungs in 19 of 43 patients diagnosed with small cell carcinoma. Nine patients had metastasis of a malignant neuroendocrine tumor and the tumor was found to originate from the gastrointestinal system in six patients.

Nine patients had metastasis of melanoma. One of these patients had signs of metastasis on his skin and another in his eyes. Twelve patients, diagnosed with malignant lymphoma of the liver, had been attending follow up for their non-Hodgkin lymphoma.

Table 4. Liver tumors metastasizing from the lungs

Diagnosis	*n*	*%*
Squamous Cell Carcinoma	27	50.00
Small Cell Carcinoma	19	35.19
Adenocarcinoma	8	14.81
Total	54	100

Cytological Features

Of patients diagnosed with squamous cell carcinoma, 93.32% had cytoplasmic keratinization. Aggregation of cells to form a flat layer and a centrally located nucleus were the other hallmarks of squamous cell carcinoma. A cell sequence, resembling a trabeculer sequence, was present in 6.31% of cases.

Molding occurred in 55% of the patients diagnosed with small cell carcinoma. Necrosis, which was the most frequent finding, was present in 75% of patients.

Cytoplasmic size of the nucleus increased in all cases of adenocarcinoma and 38.97% of cases had nucleomegali. Necrosis was present in 33.12% of cases and centrally located nuclei with a large cytoplasm were found in 21.18% of patients with metastasis of gastric adenocarcinoma (Figure 1,2). A signet cell structure was present in 47.36% of these cases. There were cytoplasmic vacuoles in all cases, suggesting cytoplasmic mucine.

All patients with metastasis of colonic carcinoma had nucleomegali, and nuclei were arranged side by side to form a palisadic sequence in 95.22% of patients. Infiltration of neutrophils into tumor cells and cytoplasmic vacuolization were observed in 85.72% and 100% of these cases respectively.

Nuclei were located eccentrically in cases of mucinous adenocarcinoma. Cytoplasmic and free mucines were observed in all cases, and cytoplasmic mucine was present in 62.53% of eight cases

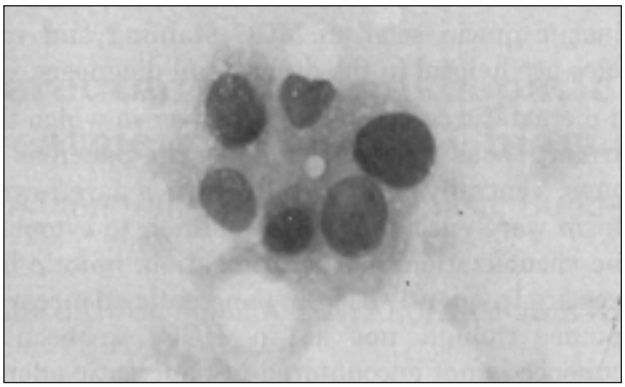

Figure 3. Metastasis of invasive ductal carcinoma (x400;MGG).

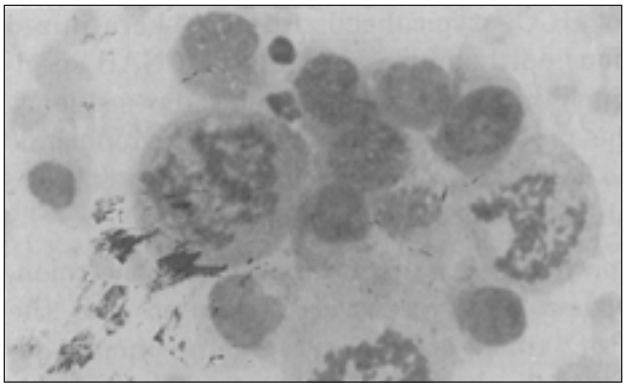

Figure 4. Mitotic figures frequently seen in adenocarcinoma of the pancreas (x1000; MGG).

in which primary tumor was located in the gallbladder.

In 17.63% of patients with adenocarcinoma of the pancreas, the cells had a large cytoplasm and a centrally located nucleus. The nucleus was located eccentrically in the other cases; 88.27% of the cases had cytoplasmic mucine and 23.59% keratinization. Mitotic figures were frequently found in patients with metastasis of pancreatic carcinoma (Figure 3).

As to invasive ductal carcinoma of the breast, the cells had a centrally located nucleus and large cytoplasm in 15.4% of the cases (Figure 4). Nucleomegali and cytoplasmic mucine were present in 87.25% and 43.64% of these cases respectively. Large cytoplasmic size and cytoplasmic vacuoles were identifiable features in ovarian tumors and seen in 58.33% of the cases.

The nucleus was located eccentrically and nucleomegali and cytoplasmic vacuoles were present in all patients with metastasis of renal cell carcinoma. It was striking that the cells were small in patients with metastasis of prostatic adenocarcinoma, and the nucleus was located in the center of the cell in half of these cases.

Six patients were diagnosed with adenocarcinoma of the suprarenal cortex. The nucleus was eccentrically located in all these cases. Pleomorphism, detected among atypical cells in blood films of these patients, was striking. In one case, hyaline like material was observed in the cytoplasm.

Nine patients were diagnosed with malignant melanoma of the liver. Melanin was detected in 77.85% of these cases, atypical lymphoid infiltration was diffuse in the blood films and there were intact hepatocytes between these infiltrations.

DISCUSSION

It is possible to make the diagnosis of all space-occupying lesions in the liver by FNAB under the guidance of imaging techniques, regardless of the size of the lesion. In addition, FNAB allows differentiation of benign from malignant lesions, determination of whether the lesion is primary or metastatic in a shorter time than biopsy only and is less costly (1-6). Although metastatic cancers cause multiple masses, they cause solitary masses in 10% of cases.

One of the most important problems encountered in the diagnosis of hepatocellular carcinoma is differentiation of atypical hepatocytes from metastatic adenocarcinoma by FNAB (14-16). Atypical cells, demonstrated by FNAB, are the cells whose nuclei are centrally located and which have a large cytoplasm. These cells are arranged to form a cordon.

The most frequent malignancy of the liver is metastatic tumor (1,19). In fact, a metastatic tumor was found at autopsy in 40% of patients with a malignant tumor (20). Cancer of the lungs, pancreas, colon, breast and stomach in adults and neuroblastoma, Wilm's tumor and rabdomyosarcoma in children frequently metastasize to the liver (20). Metastases of carcinomas whose primary foci are not determined have been reported to originate from the lungs and pancreas at autopsy series (1). In our series, the ratio of primary to metastatic liver tumors was 1:2. Of all tumors whose primary focus was determined, metastasis of pulmonary tumors was the most frequent. Squamous cell carcinoma, small cell carcinoma and adenocarcinoma comprised 50%, 35.19% and 14.81% of pulmonary tumors respectively. In

cases of HCC, atypical cells resemble keratinized squamous epithelium, especially on FNAB specimens including necrosis and trabecular sequence and the presence of bile pigments, cytoplasmic hyaline bodies, intranuclear inclusions and nucleomegali can lead to the diagnosis of HCC.

In all patients with adenocarcinoma of the colon, the nucleus was eccentrically located and the ratio of nucleus to cytoplasm increased. Nucleomegali, observed in all cases, naked nuclei, frequently encountered necrosis (66.72%) and infiltration of polymorphonuclear leucocytes (85.75%) aided diagnosis. A palisadic sequence of the nucleus was observed in most cases (95.27%). Adenocarcinoma of the colon is there fore unlikely to be mistaken for HCC.

In a small number of patients with metastases of breast carcinoma the nucleus is centrally located. Cytological features in these cases are similar to those in cases of HCC. In fact, the cytoplasm is large in both cases, and the trabecular cell sequence encountered in patients with metastatasis of breast carcinoma resembles the structural cell sequence in cases of HCC. The same cell sequence can be seen also in a certain proportion of patients with metastasis of gastric adenocarcinoma (21.16%). Therefore, adenocarcinomas of the stomach can be confused with HCC, but cytoplasmic mucin seen on MGG staining and vacuoles are helpful in the differential diagnosis.

In metastatic carcinomas of the liver in which the primary focus was thought to be the pancreas or lungs, centrally located cells with a large cytoplasm were encountered. In addition to cytoplasmic vacuolization and keratinization, mitotic figures are frequently seen in pancreatic adenocarcinomas, though not so in HCC. Trabecular sequence is not encountered in pancreatic adenocarcinomas.

In renal cell carcinoma, eccentrically located nucleus and uniform vacuoles in the cytoplasm can be used to make a differential diagnosis although the cytoplasm and nucleus are large as in HCC.

In conclusion, FNAB is an invaluable diagnostic tool which can be used with clinical examination and laboratory investigations in the differentiation of primary metastatic tumors of the liver. It is inexpensive, easy to perform and has no side-effects. Malignant tumors, which can be mistaken for HCC, are invasive ductal carcinoma, renal cell carcinoma and squamous cell carcinoma because their cellular features and sequences may be similar.

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