Case report

CUTANEOUS METASTASIS FROM HEPATOCELLULAR CARCINOMA. REPORT OF A CASE WITH REVIEW OF THE LITERATURE

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ABSTRACT

A case of solitary cutaneous metastasis in the genital area originating from liver cell carcinoma in an old woman is described. The rarity of the occurrence as regards both the primary source and the secondary site of metastatic deposits is stressed. The morphologic and immunohistochemical features which assisted in the correct diagnosis are also outlined, and a detailed review of the literature performed.

KEY WORDS
cutaneous metastasis, hepatocellular carcinoma, vulva

INTRODUCTION

The incidence of the various tumors metastatic to the skin in men and women commensurate well with the frequency of occurrence of the primaries.

Liver cell carcinoma (LCC) is a relatively rare neoplasm accounting for 1.4 % of all internal malignancies in USA and for 0.9 % in U.K. (14). In Italy its relative incidence rate amounts to 5-20 cases/100.000 people/year ("intermediate incidence") (1a). Therefore, accordingly, metastatic deposits in other sites are rare as well.

LCC metastasizes either by blood stream or lymphatic channels capable of producing widespread metastases to many sites. Lungs, adrenal glands, bones, kidneys, pancreas, spleen, colon, lymph nodes, gallbladder, diaphragm, heart, and brain are on record (10-12, 15, 18). Skin metastases are very unusual for LCC (9, 17).

We describe a case of solitary metastasis occurred in the genital area of an old female patient.

CASE REPORT

An 80-year-old white woman was hospitalized (Department of General surgery, Ruvo di Puglia, Bari, Italy) complaining of pain and discomfort in the genital area due to the onset of a nodule which appeared 1 month prior to the admission. At physical examination the tumor nodule was located on her left labium major bordering the mucocutaneous edge, ulcerative and violaceous in appearances, and firm at palpation. The lesion was locally excised on the clinical suspicion of a primary skin tumor and the surgical specimen

sent to the Anatomic Pathology Department of "Casa Sollievo della Sofferenza" Hospital (S. Giovanni Rotondo, Foggia, Italy) for histological examination.

The lesion was composed of trabecular cords of tightly packed large eosinophilic cells with prominent nucleoli, separated by thin collapsed or dilated capillaries bordered by flat endothelial cells, thus suggesting an overall sinusoidal pattern (Fig. 1 - 2). Scattered giant multinucleated neoplastic

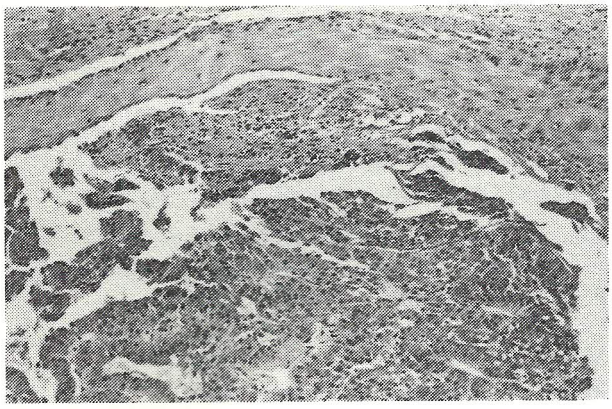

Fig. 1 The tumor is located in the lower half of the picture, while the squamous epithelium is clearly visible at the top. (H.E. x 105)

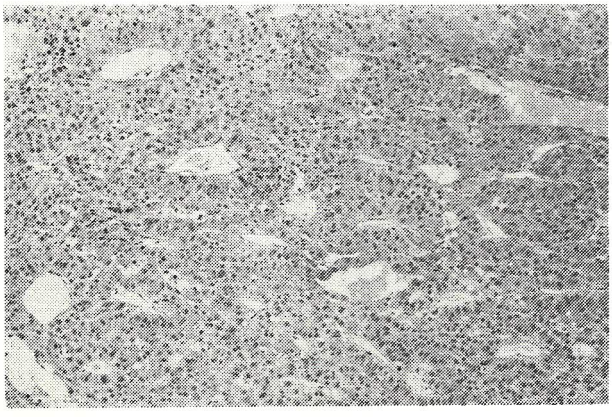

Fig. 2 The overall trabecular growth pattern of tumor. The neoplastic cell cords are separated by prominent sinusoidal spaces lined by flat endothelial cells. (H.E. x 105)

cells were also seen (Fig. 3). The cell cytoplasm appeared somewhat granular, focally showing weakly PAS-positive hyaline globules (Fig. 4), and some refractile irregular inclusion-like material of the Mallory's hyaline type.

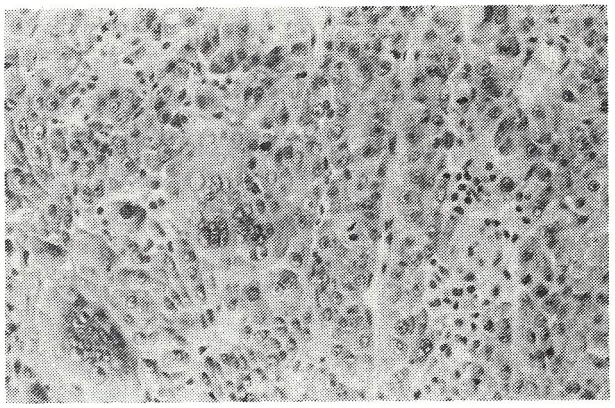

Fig. 3 Two huge multinucleated neoplastic cells are seen toward the left. (H.E. x 240)

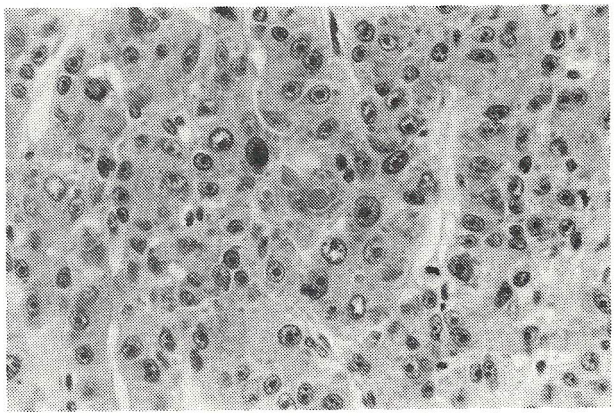

Fig. 4 Moderately differentiated neoplastic hepatocytes displaying prominent nucleoli. In the center many globular hyaline bodies of varying size are shown. (H.E. x 410)

Based upon these findings a metastasis from LCC was first strongly favoured, but the histopathologic differential diagnosis included also an amelanotic melanoma, and a primary apocrine carcinoma of adnexal glands.

Immunohistochemically the neoplastic cells showed reactivity with antisera against intermediate filaments of cytokeratins (clone: MNF-116, Dakopatts, Glostrup, Denmark), against the epithelial membrane antigen (EMA) (clone E29, Dakopatts, Glostrup, Denmark) and-focally-against alfa-fetoprotein (AFP) (Cambridge Research Laboratories, Cambridge, MA, USA) (Fig. 5).

TABLE I

CUTANEOUS METASTASES FROM LIVER CELL CARCINOMA. REPORTED CASES.

Au.	Ref.	Year	No Cases	Sex	Site	No Mts	Pres. Sign
Gates	(7)	1937	5*	2M/3F	1 Head 3 Trunk 1 Extr.ty	?	?
Viranvunatti et al.	(22)	1959	1	?	Scalp	?	?
Epstein	(6)	1964	1	?	?	?	?
Kahn et al.	(9)	1971	1	M	Head	m	Yes
Brownstein and	(4)	1972	1	?	?	?	?
Helwig			1	?	?	?	?
			1	?	?	?	?
Helson and Garcia	(8)	1975	1	F	Trunk	m	No
Reingold et al.	(18)	1978	1	M	Scalp	m	Yes
			1	M	Scalp	m	Yes
Bennet et al.	(2)	1982	1	M	Chest	s	Yes
Muretto and Del Fiasco	(13)	1990	1	M	Diss.	m	?
Present case		1993	1	F	Vulva	s	Yes
TOTAL CASES			17				

Key to abbreviations:.

Pres. sign = presentation sign (i.e., skin metastasis as the first clinical manifestation of liver cancer.
* = 4 cases from the previous literature; 1 case of author's own.
? = not stated by the author.
+ = mixed hepatoma (liver cell carcinoma plus cholangiocellular carcinoma).
Extr. ty = extremity
F = female
M = male
m = multiple
s = solitary

No immunoreactive stain was revealed as regards intermediate filaments of vimentin (clone: V9; Dako, Glostrup, Denmark), S100 protein (Enzo Biochem Inc, Raritain, NJ, USA), melanoma-associated antigen (clone: HMB-45, Enzo Biochem Inc, Raritain, NJ, USA), and the gross cystic disease fluid protein-15 (GCDFP-15) (Signet Laboratories

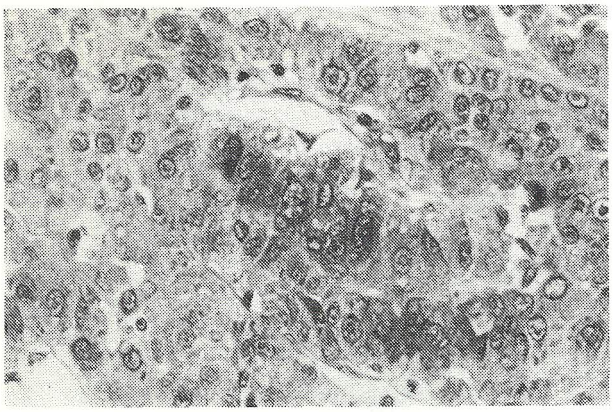

Fig. 5 Cell cytoplasm focally darkly stained with antiserum anti-AFP. (Streptavidin-Biotin complex stain x 410)

Inc, Dedham, MA, USA). On the basis of such a depicted immunophenotypic profile the diagnosis of LCC metastasis was established. Subsequently on a revisited clinical history it came up that the patient was suffering from a longstanding postinfectious hepatitis liver cirrhosis which at the time of the her hospitalization showed current progression.

In fact a 8 cm sized tumor mass was detected on liver echoscan in the right lobe and the serum AFP level was 4560 ng/ml (normal 0 to 20 ng/ml). No additional metastatic seedings were discovered on a total body scan. Furthermore on reviewing the histologic slides it was possible to recognize even some granules of bile pigment. The patient was then given appropriate courses of chemotherapy.

COMMENT

LCC developing skin metastases has been rarely reported (2, 4, 6, 7, 8, 9, 13, 18). Skin metastasis from LCC is almost a curiosity: in fact, putting together large series of cutaneous metastases from other sites including skin itself (3, 21) and series excluding skin primaries (17, 20) some other authors (5) collected 4 such cases recorded out of a total of 1489. This figure amounts to 0,2 %, which is a very light contribute, if we consider the incidence of other internal cancers.

From the milestone paper by Brownstein and Helwig (3) on the incidence of skin metastases from the various organs in men, lung, large bowel, oral cavity, kidney and stomach, were respectively the primary sources in 24 %, 19 %, 12 %, 6 % and 6 %, whilst among women breast, large bowel, lung, and ovary resulted in 69 %, 9 %, 4-5 %, and 4-5 % respectively. Up to date only 17 cases have been described with the head as the most favourite localization, followed by trunk and finally extremities (Table I). Cutaneous metastases from LCC can be solitary as well as multiple, either in form of a forerunning herald of metastatic disease or concurrent with or subsequent to a widespread dissemination to other sites, with an invariably short interval survival time prior to death of very few months.

This is one of the few reported cases in which the cutaneous metastasis constituted the presenting sign of LCC, and the only one in which the localization has been observed on the genital skin, which-on the other hand-is also the rarest site even when considering skin metastases as a whole (3). The most compelling questions pathologists have to face when dealing with a malignant skin tumor are: is it a primary or a secondary tumor? and which is the source from which it originated?

The correct diagnosis of a neoplasm as a metastatic seeding and its differentiation from various primary skin tumors is obviously important for prognostic significance, and the correct identification of the primary source has enormous importance for diagnostic and therapeutic aims as well.

As for the presented case the definite diagnosis was based upon the almost specific AFP immunostaining on tissue sections in the neoplastic cells and mostly on the finding of some bile pigment in the intercellular spaces, which absolutely represents a (morphologic) specific marker shared by no other neoplasia. Eventually the very high level of serum AFP was contributory too in a pathognomonic way (16). Thus the liver needle biopsy of the primary cancer was not taken, so avoiding the patient some more discomfort and risk. This case because of the unusual site of presentation should have been particularly intriguing and challenging, if some peculiar morphologic and immunohistochemical features had not resulted so decisive.

REFERENCES

1. Antony PP. Tumors and tumor-like lesions of the liver and biliary tract. In Pathology of the liver. MacSween RNM, Anthony PP,. Scheuer PJ. edsChurchill Livingstone, Edinburgh, 2nd edit, 1989

2. Bennet A.J., Kalra J.K., Cortes E.P.. Hepatocellular carcinoma. Manifestation as a chest wall metastasis. Arch Dermatol 1982; 118:69-70

3. Brownstein M.H., and Helwig E.B.. Patterns of cutaneous metastasis. Arch Derm 1972; 105:862-868

4. Brownstein M.H., Helwig E.B.. Metastatic tumors of the skin. Cancer 1973; 29:1298-1307

5. Chimenti S. Metastasi cutanee da neoplasie degli organi interni. CIC Edizioni Internazionali. Roma 1990, p. 34-35

6. Eppstein S. Primary carcinoma of the liver. Amer J Med Sci 1964; 247: 137-144

7. Gates O. Cutaneous metastases in malignant disease. Amer J Cancer 1937; 30: 718-730

8. Helson L., Garcia E.J.. Skin metastases and hepatic cancer in childhood. NY States J Med 1975; 5: 1728-1730

9. Kahn J.A., Sinhamohapatra S.B., and Schneider A.F.. Hepatoma presenting as a skin metastasis. Arch Derm 1971; 104: 299-300

10. Kay C.H.. Primaryhepatic cancer: Review of 96 cases. Arch Intern Med 1964; 113: 96-103

11. Lopez-Corella E., Ridaura-Sanz C., Albores-Saavedra J: Primary cancer of the liver in Mexican adults. Cancer 1968; 22: 678-685

12. Mac Donald R.A.. Primary carcinoma of the liver: A clinicopathological study of 108 cases. Arch Intern Med 1957; 99: 266-279

13. Muretto P, Del Fiasco S. Metastasi cutanee da carcinoma epatocellulare. Quaderni di istopatologia dermatologica. Vol. 8, p. 68, 1990, Torino

14. Okuda K, Hiroaki O. Primary liver cell carcinoma. In Textbook of liver hepatology voll. 1-2. Benhaumu P., Bircher J, Rizzetto M and Rodes J eds. Oxford University Press 1991 p. 1021

15. Parker J.C., Dahlin D.C:, Stauffer M.H.. Malignant hepatoma: Evaluation of surgical (including needle biopsy) material from 69 cases. Mayo Clin Proc 1970; 45: 25-35,

16. Portmann BC. Histochemistry in idiopathic assessment of liver biopsy. In: Histochemistry in Pathology. Filipe MJ and Lake BD eds. Churchill Livingstone, Edinburgh 1990, p. 230

17. Reingold I.M. Cutaneous metastases from internal carcinoma. Cancer 1966; 19: 162-168

18. Reingold I.M., Smith B.R.. Cutaneous metastases from hepatomas. Arch Dermatol 1978; 114: 1045-1046

19. San Jose D., Cady A., West M., et al. Primary carcinoma of the liver: Analysis of clinical and biochemical features of 80 cases. Amer J Dig Dis 1965; 10: 657-672

20. Spencer PS, Helm TN. Skin metastases in cancer patients. Cutis 1987; 39: 119-121

21. Tharakaram S. Metastases to the skin. Int J Dermato 1988; 27. 240-242,

22. Viranvunatti V., Satapanakul C. Primary carcinoma of the liver. In World Congress of Gastroenterology. Baltimore, Williams & Wilkins Co, 1959, p 516-526

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