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Case Report

Primary Malignant Mixed Mesodermal Tumor of the Gallbladder

Report of a Case and Critical Review of Diagnostic Criteria

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Summary. A rare case of primary malignant mixed mesodermal tumor of the gallbladder arising in a 75 year old woman is reported. The previously published cases of similar tumors were reviewed in order to outline the histological features and the histogenesis. In diagnosing a malignant mixed mesodermal tumor of the gallbladder it was imperative that we excluded malignant neoplasms with multiple histological patterns. The diffuse and close intermingling of the epithelial and mesenchymal component ruled out a collision tumor. The high mitotic rate, the typical reticulin pattern and the obviously malignant osteoblasts excluded a spindle cell carcinoma with osseous metaplasia. The authors conclude that this is the first case of malignant mixed mesodermal tumor with evident osteosarcomatous areas, described in the gallbladder.

Key words: Malignant mixed tumor – Carcinosarcoma – Malignant mixed mesodermal tumor – Gallbladder

Malignant mixed mesodermal tumor (MMMT) is a rare neoplasm usually found in the uterine body and pelvic structures of müllerian origin. (Sternberg et al. 1954; Palladino and Trousdell 1969). The characteristic feature of this tumor is the admixture of carcinomatous and sarcomatous elements. The nature of the sarcomatous element is the basis for the division of MMMT into homologous or heterologous varieties. In the former the malignant stromal portion may differentiate toward the mesenchymal tissues normally seen in the organ. In the heterologous type there are also present specific malignant mesenchymal elements not normally found in the organ (such as cross striated muscle, cartilage etc.). Similar peculiar malignant mixed neoplasms have been described in many other locations. MMMT of the gallbladder is a genuine but uncommon entity whose histogenesis is still controversial; four cases have been reported previously

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(Edmonson 1962; Mehrotra et al. 1971; Higgs et al. 1973; Mansori and Cho 1980). In the present report we describe a case of primary MMMT of the gallbladder characterized by osteosarcomatous areas and review the literature of similar tumors in an attempt to define their histological and pathological features.

Case Report

A 75-year-old woman was admitted to the hospital experiencing abdominal pain and vomiting. For over a month she complained of asthenia and anorexia and she stated that she had lost 10 kg. Fifteen years previously she underwent total hysterectomy for uterine leiomyomas. Further past history was unremarkable. Liver function tests revealed an alkaline phosphatase level of 2,154 IU (normal 100–290) and γGT elevated to 70 uU/ml. (normal 28), serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, bilirubin and other laboratory measurements were within normal limits. In the right hypocondrium physical examination showed the liver to be enlarged with a hard border and a large palpable mass. Similary abdominal roengenogram and ultrasound scanning revealed a round mass, the greatest diameter being 9 cm, in the region of the gallbladder. At laparatomy the gallbladder was enormously enlarged pressing on the stomach and duodenum. Inside the lumen was filled with soft, pink, grayish tissue with haemorrhagic, necrotic areas. The polipoid growth encompassed some large rounded stones. The wall was irregular, thick and greatly adherent to the inferior surface of the liver. The lesion was interpreted as being consistent with a carcinoma of the gallbladder; however, in the view of the patient's poor physical conditions, radical surgery was not carried out. A large part of the tumor was removed and sent for histological examination and cholecystostomy was performed. Roentgenological examinations of the skeleton were negative for bone lesions. The patient was still alive 8 months later.

Materials and Methods

All the tissue was fixed in neutral buffered formalin and embedded in paraffin. Step sections were made and at least 20 sections were obtained from every block. Sections were stained with haematoxylin and eosin, periodic acid Schiff with and without diastase digestion, Gomori's reticulin stain, PTAH technique, Masson's trichrome. We used a Leitz Orthoplan, objective magnitude 40×, eyepiece GW Periplan 10×, field of view index 24 for counting mitoses (Ellis and Whitehead 1981).

Microscopical Findings

Neoplastic tissue was formed by three elements. The epithelial component exhibited glandular differentiation, the pseudoglandular structures being tubular or budded with areas of cribriform arrangement. The epithelial layer was composed of cuboid-columnar cells, with variable degree of pseudostratification. Cells showed irregular round nuclei in basal position and large clear cytoplasm. (Figs. 2 and 3). Gland lumena were filled by PAS diastase positive material. The stromal component was obviously malignant, composed of spindle cells, with blunt-ended nuclei arranged in bundles. Reticulin was abundant and surrounded individual cells (Fig. 5). The mitotic rate was high (8 mitotic figures/10 HPF) (Fig. 3) and some atypical giant cells were present. Large and evident osteosarcomatous areas were diffusely scattered in this stroma (Figs. 1 and 2). Coarse irregular osteoid and well differentiated bony trabeculae were surrounded by active atypical osteoblastic-like cells, sometimes in mitotic division (Fig. 4). PTAH technique and trichrome stain did not reveal cross-striated muscle cells. A close intermingling of 3 components was diffusely observed in all

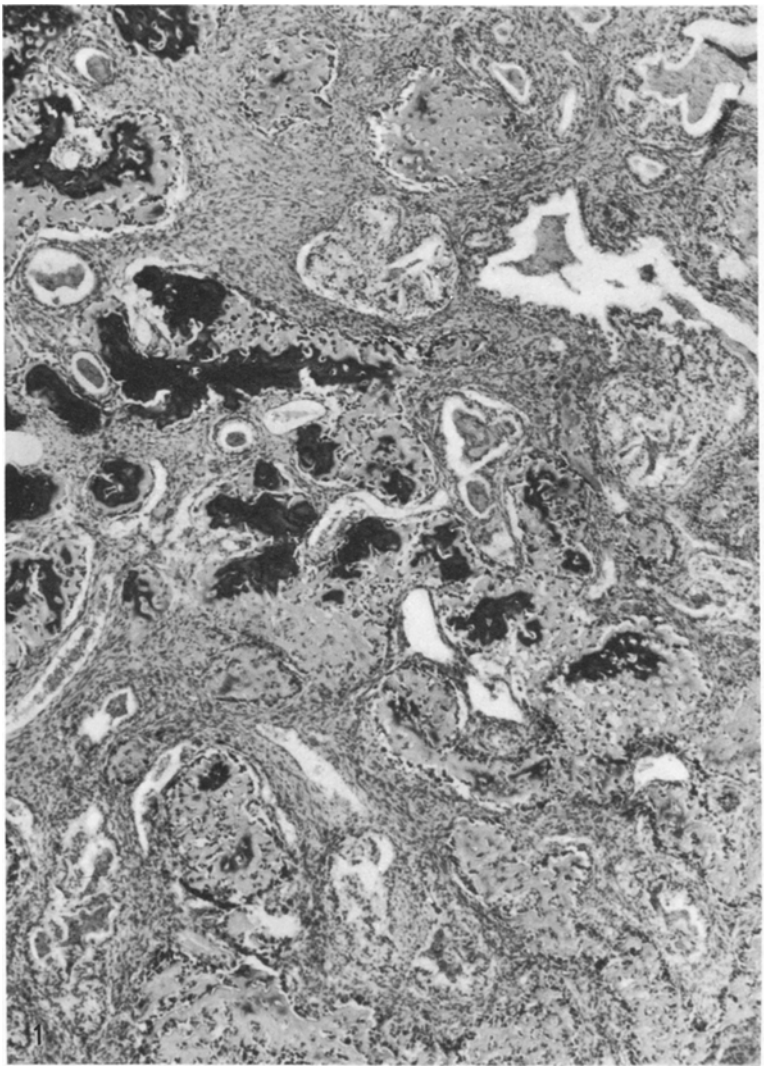

Fig. 1. Neoplastic tissue is characterised by a close intermingling of adenocarcinomatous glands, sarcomatous stroma, osteoid areas and calcified bony trabeculae. Haematoxylin-eosin × 10

the sections and everywhere the carcinomatous portions was sharply delineated from the spindle cell stroma (Figs. 1, 2 and 5).

Discussion

Malignant mixed epithelial and mesenchymal neoplasms show complex histological patterns that make recognition and classification of this group of tumors very difficult. (Hendrickson and Kempson 1980). In diagnosing malignant mixed tumors it is essential to evaluate the nature (benign, malignant), the type (epithelial, mesenchymal and metaplastic) and the architectural pattern of the tumor's

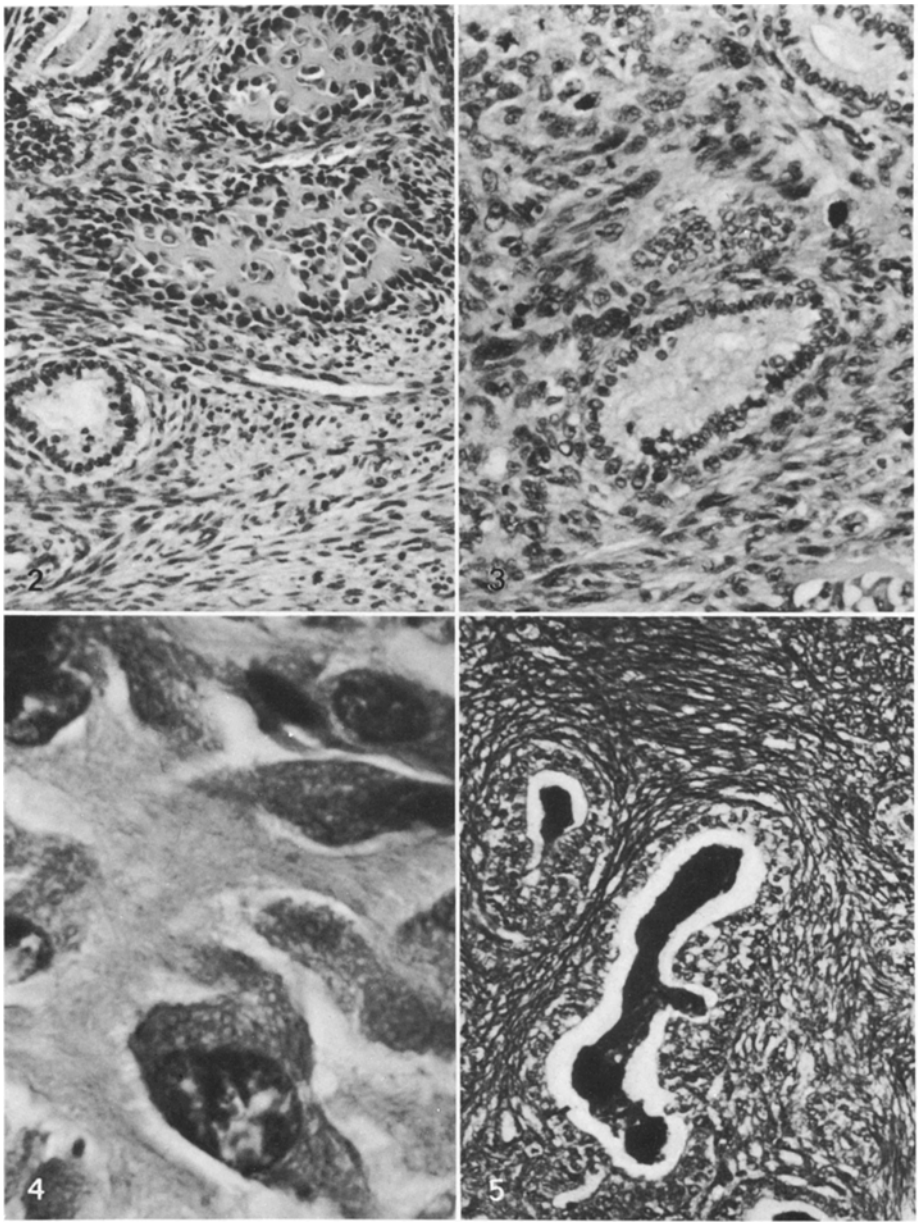

Fig. 2. Osteoid masses are surrounded by atypical osteoblastic cells. Haematoxylin-eosin ×25

Fig. 3. Numerous mitotic figures are evident, sometimes atypical. Haematoxylin-eosin ×25

Fig. 4. Osteoblastic cells show hyperchromatic irregular nuclei. Haematoxylin-eosin ×40

Fig. 5. The stromal component exhibits abundant reticulin, surrounding single cells. Reticulin stain ×10

components to avoid ambiguous nomenclature. A wide variety of terms have been used to classify malignant tumors with multiple histological patterns (carcinosarcoma, malignat mixed tumor, malignant teratoma, blastoma, malignant mixed mesodermic tumor). Carcinosarcoma is the commonly used term to describe these neoplasms, but this misused word has ended up being used to assemble totally different entities and it is now confusing and misleading (Christopherson and Richardson 1981). In fact sometimes the term carcinosarcoma was wrongly employed as synonymous with spindle cell carcinoma or to describe collision tumors. On the other hand this term does not specify the homologous or heterologous nature of the mesenchymal portion. The distinction should be useful on the basis of the slightly better prognosis connected with the former type. (Kempson and Bari 1970). Following the example of Norris and Taylor's view (1966) of uterine tumors we prefer to classify as carcinosarcoma only true malignant mixed tumors with homologous sarcomatous elements and classify the heterologous ones as MMMT wherever they are localized. In our case we were dealing with a tumor in which all the components, heterologous part included, were malignant, were present in every area and were intimately intermingled with each other, but distinct, thus we diagnosed it as primary MMMT of the gallbladder. Before assuming our tumor was a primary MMMT it was imperative to exclude the various histological appearances that may simulate it: 1) carcinoma with spindle and pleiomorphic cells simulating a sarcoma (carcinoma with sarcoma like stroma, spindle cell carcinoma, carcinoma with spindle metaplasia, pseudosarcoma); 2) collision tumor; 3) metastasis of a primary bone osteosarcoma to a carcinoma; 4) primary sarcoma with benign epithelial inclusion; 5) adenosarcoma. Spindle cell carcinomas have an element of carcinoma, frequently epidermoid, often inconspicuous, and a pleiomorphic preponderant sarcoma like component, but usually it is possible to find transition between these different areas. (Appelman and Oberman 1965; Apelman and Coopersmith 1970). In the gallbladder calcification and osseous metaplastic change are occasionally found in chronic colecystitis and therefore may be incidentally associated with an adenocarcinoma. In the present case osteoid areas and mineralized bony trabeculae were surrounded by malignant osteoblastic cells (Figs. 2 and 4). Mitotic figures (8/10 HFP) and reticulin stain pointed out the malignant nature of spindle cells resembling leiomyosarcoma cells (Figs. 3 and 5). These features allowed us to exclude spindle cell carcinoma. Collision tumors are not truly mixed neoplasms, since they develop from the contiguous growth of a carcinoma and a sarcoma, each of which originate separately (Meyer 1920). In our case all sections showed a close mingling of neoplastic glands and sarcomatous stroma; therefore a collision tumor was excluded. (Fig. 1). For the same reasons metastasis of a bone tumor to the gallbladder's adenocarcinoma appear unlikely, since no primary bone lesion was manifested clinically or radiologically. In the present case the epithelial portion was clearly malignant. The pseudoglandular structures were arranged in a cribriform pattern and were lined by cells exhibiting marked nuclear abnormalities, with atypical mitotic figures. A primary osteosarcoma with benign epithelial inclusions or an adenosarcoma were ruled out.

The literature quotes 4 reports of primary malignant mixed tumors in the gallbladder (Edmonson 1962; Mehrotra et al. 1971; Higgs et al. 1973; Mansori

and Cho 1980). In his report Higgs (1973) described only scattered foci of metaplastic osseous tissue, whereas a single tumor characterized by osteosarcomatous areas was described by Mehrotra et al. (1971). Nevertheless in his study adenocarcinomatous growth was inconspicuous and the distribution of the different components and the ichonography calls into question a collision tumor. We think our report the first well documented primary MMMT of the gallbladder, in which evident malignant osteoid tissue is presented. The association of elevated alkaline phosphatae in the absence of liver disease is an interesting finding. Similar data have been stressed by Das Gupta et al. (1968) in soft tissue osteogenic sarcoma. The histogenesis of MMMT in the female tract has always excited much speculation. The hypothesis of origin from primitive multipotential paramesonephric tissue or indifferentiated müllerian stroma does not explain similar tumors arising in different embryological derivates or the incidence in the aged. Neoplasms developed from blastomatous cells usually occur in children (malignant mixed tumor of the liver, Wilm's tumor). Perhaps it is best to admit that the histogenesis is unknown.

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