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Case report

Malignant angioendotheliomatosis (*Angiotropic lymphoma*) of the gallbladder

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Summary. We present a case of malignant angioendotheliomatosis of the gallbladder, the first reported. Diagnostic problems connected with this rare malignancy are underlined. Immunohistochemical studies were useful in providing further evidence of the lymphoid nature of the neoplasm and avoiding possible misdiagnosis. We suggest that the term "angiotropic lymphoma" might be more appropriate to define this malignancy.

Key words: Gallbladder – Malignant angioendotheliomatosis – Malignant lymphoma – Immunohistochemistry – Differential diagnosis

Introduction

Malignant angioendotheliomatosis (MAE), firstly described under the designation of "angioendotheliomatosis proliferans systemisata" by Pfleger and Tappeiner in 1959, is a rare, mostly fatal, intravascular disease characterized by a neoplastic proliferation of large, mononuclear cells within lumina of small and medium-sized vessels throughout the body.

The histogenesis of the neoplastic cells has been the object of numerous studies and controversies. However, recent reports, based on immunohistochemical studies, strongly suggest a lymphoid origin for the disease (Mori et al. 1985; Wrotnowski et al. 1985; Wick et al. 1986; Sheibani et al. 1986; Carrol et al. 1986). Thus, new terms, such as "angiotropic lymphoma" (Wrotnowski et al. 1985) and "intravascular malignant lymphomatosis" (Wick et al. 1986) were coined to describe this peculiar entity.

Clinically, vascular occlusion in a variety of organs produce a variety of symptoms but, most commonly, patients affected by MAE present with plaque-like nodules in the skin and neurological manifestations (Wick et al. 1981; Keahey et al. 1982; Bhawan et al. 1985; Wrotnowski et al. 1985; Sheibani et al. 1986; Carrol et al. 1986; Wick et al. 1986; Dominguez et al. 1986; Otrakji et al. 1988; Piérard et al. 1988).

We observed a case in which MAE was discovered by chance in the small vessels of the muscular wall and peritoneal layer of the gallbladder, apparently with no other localizations and in the absence of typical signs and symptoms. There was a mild fever and abdominal pain, which were both attributed to cholelithiasis.

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Case report

The patient, a 68-year-old woman, entered a surgical department in April 1989 with mild fever (37.5° C) and abdominal discomfort. She had no other symptoms and her physical and laboratory findings were unremarkable. Abdominal ultrasonography disclosed cholelithiasis and, consequently, the patient underwent cholecystectomy a few days later.

Histological examination of the surgical specimens stained with haematoxylin and eosin revealed a neoplastic vascular infiltration in both the muscular wall and the peritoneal layer of the gallbladder, whereas the mucosa showed only a mild inflammatory reaction. Small vessels and capillaries (Fig. 1) were found filled and frequently distended with large, round to oval neoplastic cells with scanty cytoplasm, clear nucleus and one or more nucleoli. The mitotic rate was low. In many instances, red cells and small thrombi were intermingled intraluminally with neoplastic cells. Extraluminal localizations were not observed.

Morphologically, the histological picture suggested a lymphoid proliferation with a peculiar tropism for microvasculature, although it was not possible to exclude both vascular metastatic spread of an occult primary carcinoma or a malignant epithelioid haemangioendothelioma. In order to establish the exact nature (lymphoid, epithelial or endothelial) of the neoplastic cells, an immunohistochemical study on paraffin-embedded sections was performed.

Using the peroxidase-antiperoxidase method, the cells were tested for the presence of epithelial membrane antigen (EMA), cytokeratins, factor-VIII-related antigen, common leucocyte anti-

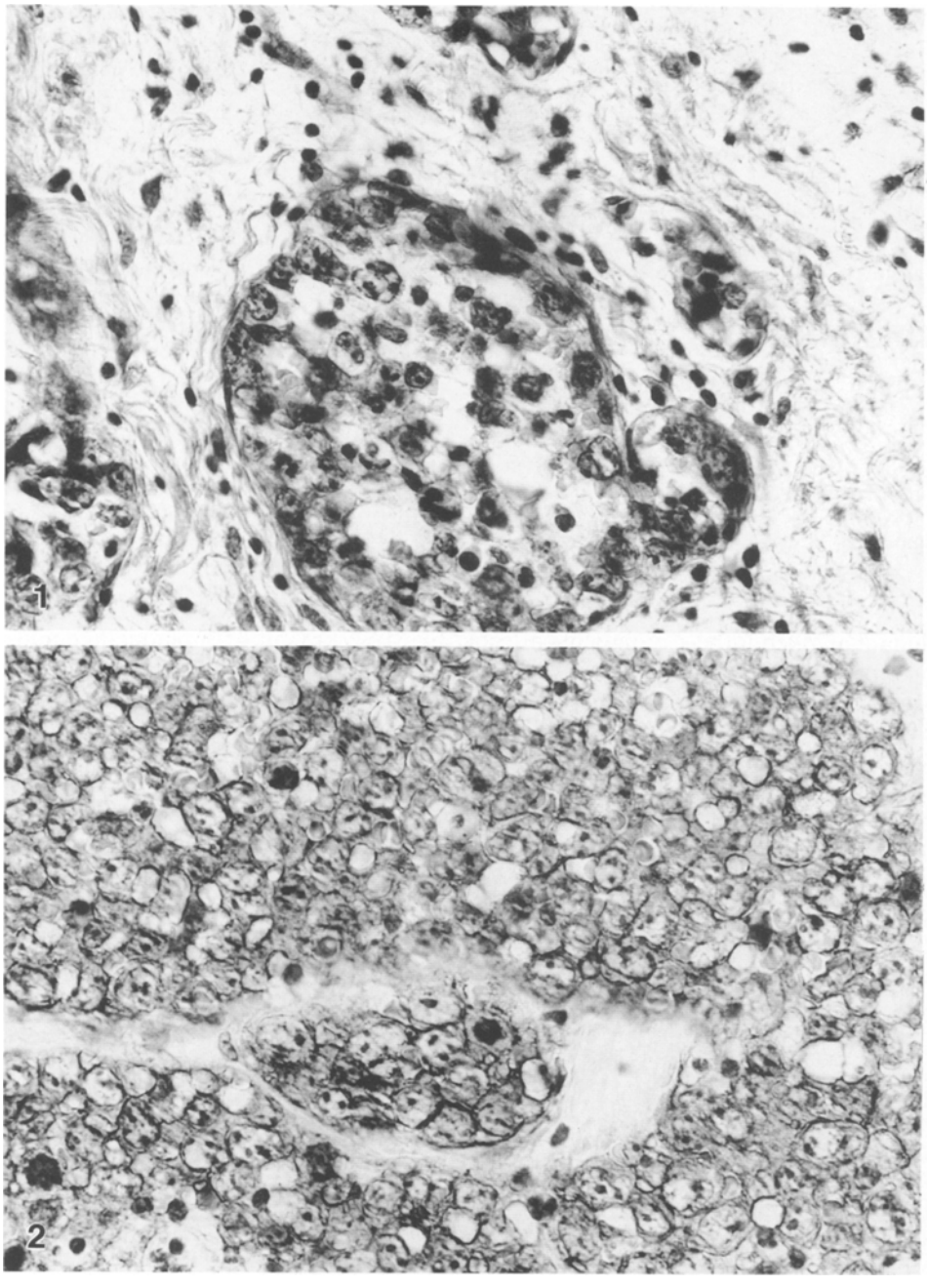

Fig. 1. Small vessels filled with neoplastic cells in the muscular wall of the gallbladder (Hematoxylin and eosin, original magnification ×40)

Fig. 2. Neoplastic cells in a vessel showing strong positivity for pan-B-cell markers (PAP, original magnification ×40)

gen (CLA), pan-B-cells marker (L26) and pan-T-cells marker (UCH-L1).

Neoplastic cells reacted positively both with CLA and L26 (Fig. 2), whereas they were completely negative with UCH-L1, EMA, cytokeratins and factor-VIII-related antigen. The gallbladder lining epithelium stained positively both for EMA and cytokeratins, providing an internal positive control. Intracapillary focal positivity for pan-T-cell markers was also observed, due to the presence of reactive T-lymphocytes intermingled with neoplastic B-cells.

A diagnosis of MAE (angiotropic lymphoma) was made.

Discussion

Although a wide variety of malignant tumours may arise in the gallbladder, over 98% of them are adenocarcinomas. Other types include carcinosarcomas, rhabdomyosarcomas, and leiomyosarcomas (Albores-Saavedra and Henson 1986). Malignant lymphomas of any type may infiltrate the gallbladder and this usually occurs as a part of a generalized process (Van Slyck and Schuman 1972). Primary malignant lymphomas of the gallbladder are exceedingly rare (Botha and Kahn 1974), thus lymphomas discovered in cholecystectomy specimens should be considered to be secondary and a diagnosis of primary lymphoma should be made only by careful exclusion (Gillespie et al. 1977).

We report a case in which neoplastic cells were found filling the microvasculature of the muscular wall and peritoneal layer of gallbladder exclusively, with apparently no other localizations. Morphologically, the fea-

tures of the malignant cells suggested a lymphoid nature, although both a metastatic carcinoma of uncertain origin and a malignant epithelioid haemangioendothelioma were taken into account in the differential diagnosis. The failure of the case to manifest immunoreactivity for EMA and cytokeratins strongly favours a non-carcinomatous origin. Malignant epithelioid haemangioendothelioma was also excluded on morphological grounds. The lymphoid nature of the lesion was confirmed by the immunohistochemical demonstration of both CLA and pan-B-cells markers in the cytoplasm of the neoplastic cells, whereas factor-VIII-related antigen was not demonstrated.

The angiotropism of the neoplastic process suggested the diagnosis of MAE. Previous reports have suggested an endothelial origin, because of the exclusively intravascular localization of neoplastic cells and the intimate association of neoplastic cells with endothelial lining (Petito et al. 1978; Wick et al. 1981; Fulling and Gersell 1983; Arnn et al. 1983). Another interpretation was that MAE could result from vascular dissemination of an occult primary carcinoma (Dolman et al. 1979), but there are no ultrastructural or immunohistochemical data to verify this assumption. Recent studies, based on immunophenotypic characterization of the neoplastic cells, have provided strong evidence for the lymphoid nature of MAE. An intense positive reaction of the neoplastic cells with CLA has been reported by many authors (Wrotnowski et al. 1985; Mori et al. 1985; Wick et al. 1986; Carrol et al. 1986; Sheibani et al. 1986; Otrakji et al. 1988). In particular, Mori et al. (1985) and Theaker et al. (1986) found that neoplastic cells are in the B-lymphocyte lineage. Sheibani et al. (1986) reported three cases of MAE, two of which presented a predominant phenotype for B-cell lymphomas, the remaining being consistent with a T-cell-derived lymphoma. Otrakji et al. (1988) studied a case of MAE by Southern-blot hybridization analysis, showing clonal rearrangements of the immunoglobulin heavy-chain gene. This strongly suggests B-lymphocyte origin of the disease.

In the present case, we demonstrated a strong immunoreactivity of neoplastic cells both for CLA and pan B-cell markers. Since there is immunohistochemical evidence that MAE is not a malignant endothelial cell neoplasm but actually a unique form of intravascular malignant lymphomatosis, the term "malignant angioendotheliomatosis" appears to be unsatisfactory. According to Wrotnowski et al. (1985) and Sheibani et al. (1986), "angiotropic lymphoma" is more appropriate term for the disorder.

MAE has been divided into three categories: (a) a benign, reactive, and self-limiting cutaneous form; (b) a progressive form originating in the skin with eventual fatal visceral involvement; (c) an aggressive, rapidly fatal form originating in the internal organs (Wick et al. 1981; Arnn et al. 1983; Gupta et al. 1986). MAE is an unsatisfactory term to define a disease which could present with a benign clinical course. A reassessment of MAE as an "angiotropic lymphoma", allows the self-limiting form to represent a smoldering process confined to the skin, such as is sometimes seen in lymphomas (Bawhan 1987).

As in the present case the malignancy was discovered by chance, the involvement of other organs and the exact extent of the neoplastic process are not known. However, given the site and the histological features, it seems reasonable to consider our case to be a high-grade malignant lymphoma.

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