Histopathology

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Lesson of the Month

Metachronous double-hit by transarterial chemoembolisation (TACE) with fotemustine inducing dysplasia-like atypia in the gallbladder and stomach—A diagnostic pitfall

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Case summary

A 41-year-old female was diagnosed with ocular malignant melanoma in May 2020. In August 2021, she presented with hepatic metastases affecting both lobes with lesions measuring up to 12 mm in diameter. Transarterial chemoembolisation (TACE) with fotemustine was started in September 2021. Twelve days after the first course, the patient presented with vague abdominal pain and elevated liver enzymes. Computed tomography scan revealed subacute cholecystitis with perforation and suspicion of pericholecystic abscess. An emergency cholecystectomy was performed. Subsequent second and third TACE courses were uneventful. Eight days after the completion of the fourth course, the patient was readmitted with nausea, vomiting, and epigastric pain. An upper endoscopy revealed a large ulcerated lesion, extending from the corpus to the duodenal bulb (Figure 1). The clinical differential diagnosis included a primary gastric cancer versus metastatic melanoma. Multiple biopsies were obtained. The patient is currently well with conservative treatment.

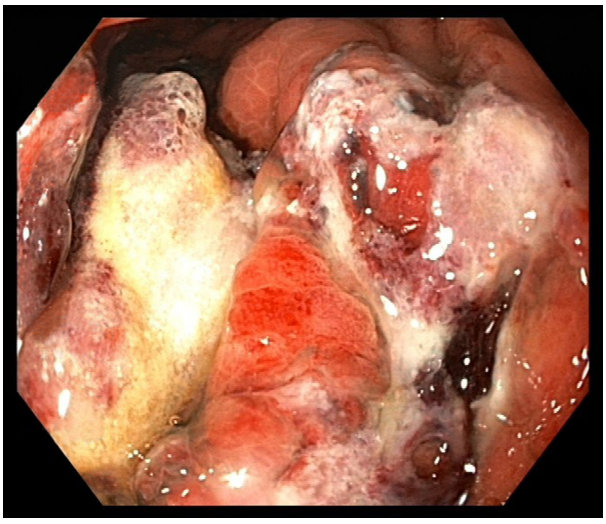

Figure 1. Endoscopy shows bizarre and irregular swelling of the gastric mucosa bordering a huge ulcer that extended from the corpus into the duodenum.

Histology

The gallbladder specimen showed gangrenous cholecystitis with widespread fibrinoid necrosis of medium-sized arteries (Figure 2A). The residual epithelium showed reactive changes. The cells were enlarged, with abundant vacuolated cytoplasm and moderately pleomorphic nuclei with distinct nucleoli (Figure 2B,C).

The gastric biopsies revealed amorphous necrotic debris. The residual viable mucosa showed enlarged crypts with ballooning cells in the upper half, characterized by mild to moderate nuclear atypia. Nuclear hyperchromasia was not observed, and the nuclear/cytoplasmic ratio was maintained (Figure 2D). Biopsies from the deep gastric glands showed severe nuclear atypia with marked pleomorphism, hyperchromasia, and loss of polarity, along with increased cytoplasmic eosinophilia (Figure 2E). Mitotic figures were not identified and cellular proliferation was limited as indicated by a low Ki67 labelling index (<5%). Accentuated p53 expression was noted in the atypical cells, but was consistent with a wild-type pattern (Figure 2F). No gastric primary tumour and no metastatic melanoma were seen.

Comment

Malignant melanoma metastatic to the liver is frequently managed with local ablative therapies such as TACE, which delivers a high dose of chemotherapy agents to the metastatic tumour but is associated with low systemic toxicity. Fotemustine is a nitrosourea alkylating agent that may be used in this setting.[1]

However, TACE is not without potential complications. Postembolisation syndrome is a side effect, characterized by fatigue, fever, abdominal pain, and elevations of liver enzymes. It usually resolves with supportive treatment. Gastroduodenal ulcers and cholecystitis are rare complications of TACE, and may be explained by the shared origin of the hepatic and gastroduodenal arterial supplies and by the propensity for reflux of chemotherapeutic agents into the cystic artery.[2]

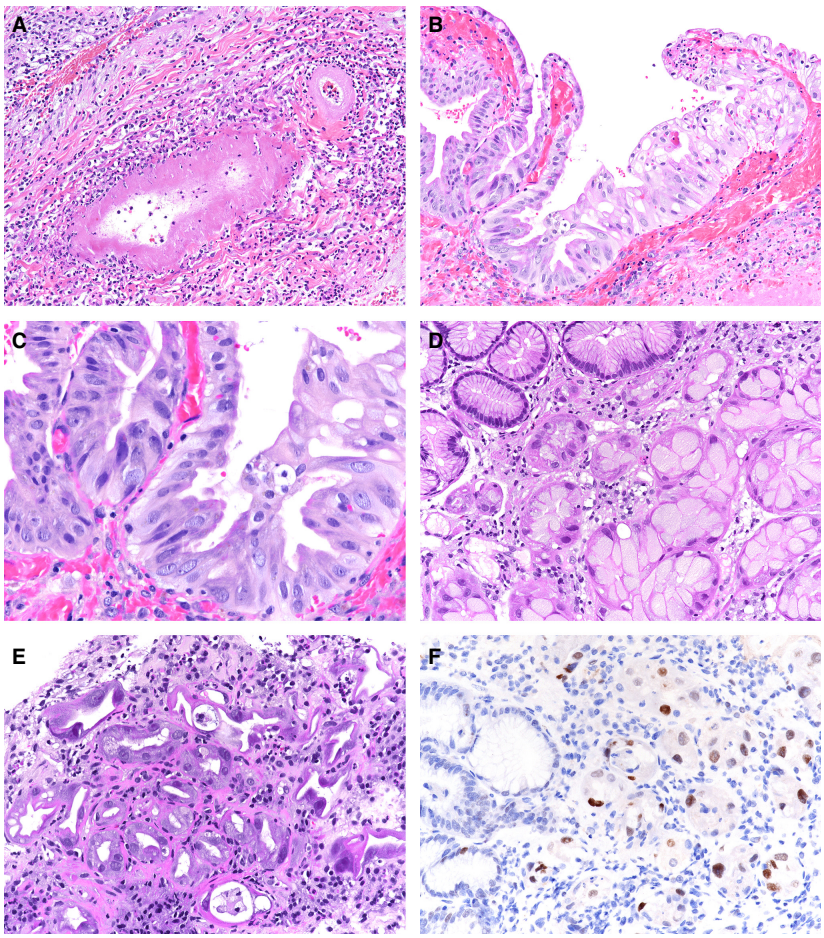

Figure 2. **A,** The gallbladder specimen shows fibrinoid necrosis of medium-sized arteries. **B,** The epithelial lining of the gallbladder includes areas of large cells with abundant clear to vacuolated cytoplasm and pleomorphic nuclei with distinct nucleoli. **C,** Nuclear atypia of the gallbladder mucosa at higher magnification. **D,** Within the gastric epithelium, atypical ballooning cells are observed in the upper half of the gastric glands; note the normal epithelium included for comparison in the upper left corner of the image. **E,** Severe cellular and nuclear atypia at higher magnification in the deep gastric glands. **F,** Nuclear overexpression of the tumour suppressor protein p53 is present in the affected cells.

Cholecystitis is usually mild and treated conservatively, although necrosis with perforation and peritonitis can occasionally be observed.[3] Chintalapati *et al.*[4] reported a patient who developed gastric and duodenal ischaemia after TACE for hepatocellular carcinoma. The histological images included in that case report demonstrate pure ischaemic injury.

In contrast, our case shows marked atypia of the gallbladder and gastric epithelium that exceeds what is typically seen in the setting of ischaemic injury and may be mistaken for dysplasia and/or malignancy. Cytoplasmic ballooning and nuclear polymorphism may be explained by drug toxicity. Specifically, fotemustine causes interstrand crosslinking of DNA, which prevents DNA replication, and ultimately leads to apoptosis. The overexpression of the tumour suppressor protein p53 in the gastric epithelium suggests that apoptosis occurs in a p53-dependent manner. Interestingly, Ki67 labelling was low in our case. This may be attributable to the fact that the highest levels of nuclear Ki67 staining are reached during the M phase of the cell cycle, which the epithelial cells failed to enter, owing to the drug effect.

Overexpression of p53 in non-neoplastic cells has been reported in ischaemic bowel disease, particularly within the withering crypts, which show marked nuclear atypia. The finding has been related to hypoxic cellular injury and subsequent attempts to regulate cell cycle progression in stressed cells or cells with DNA damage.[5]

In conclusion, pathologists need to be aware of diverse manifestation of iatrogenic injury to the gastrointestinal tract, as they may mimic dysplasia or carcinoma. Bizarre nuclear atypia in the setting of a maintained nuclear/cytoplasmic ratio and a lack of mitotic activity favour non-neoplastic changes. Overexpression of p53 may occur in the setting of reparative changes due to drug toxicity, and should not be mistaken for evidence of p53 gene alteration.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

A. Varelas: performed the histology and wrote the manuscript. E. Bruckner: performed the endoscopy and reviewed the manuscript. B. Kővári and G. Lauwers: reviewed the histology and the manuscript. C. Langner: performed the histology and wrote the manuscript.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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