Rare disease

Primary signet ring cell carcinoma of gall bladder: report of an extremely rare histological type of primary gall bladder carcinoma

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Summary

Signet ring cell carcinoma is an extremely rare type of gall bladder carcinoma composed overwhelmingly (90%) of signet ring cells. It is necessary to exclude a gastric or colonic signet ring cell carcinoma secondarily involving the gall bladder. The primary aim of this case report is to describe the histopathological aspects of this tumour. Primary signet ring cell carcinoma of gall bladder shows dysplastic surface gall bladder epithelium with infiltration of gall bladder wall. It is also necessary to exclude benign signet ring change, which sometimes occurs in the gall bladder. However, it is always confined to the mucosa and does not infiltrate the wall. This case showed grossly diffuse thickening of the gall bladder wall and dysplastic surface epithelium of the gall bladder on histology, with sheets of signet ring cells infiltrating full thickness of the wall. It is also necessary to exclude benign signet ring cell change, which sometimes occurs in the gall bladder. However it is always confined to the mucosa and does not infiltrate the wall.

BACKGROUND

Little is known about this histological subtype of gall bladder carcinoma.¹ However, some authorities believe that this variant accounts for 3% of all malignant gall bladders tumours.² These tumours show a growth pattern (linitis plastica appearance) similar to that seen in gastric signet ring cell carcinoma.³ Sometimes conventional adenocarcinoma may be seen admixed with signet ring cells. We report a case of signet ring cell carcinoma of the gall bladder occurring in a 53-year-old woman from the Northern Pakistani region of Swat. The primary aim of this case report is to describe the histopathological and immunohistochemical aspects of this rare variant.

CASE PRESENTATION

The patient, a 53-year-old woman presented with pain in the right hypochondrium that had persisted for several years. On ultrasound (the results of which were mentioned on her histopathology request form), a thick-walled gall bladder with evidence of multiple gallstones was seen. We do not know the specific reasons or symptoms that led the surgeon to perform a cholecystectomy at this point of time. The patient underwent an open cholecystectomy. A thick-walled, acutely inflamed gall bladder (according to surgical notes mentioned on her histopathology request form) containing multiple stones was removed. No suspicion of carcinoma was raised by the surgeon.

INVESTIGATIONS

We received an already opened gall bladder in formalin, measuring 5.5 × 2.5 cm in diameter. No clip was seen at the surgical margin. The procedure appeared to be an open rather than a laparoscopic cholecystectomy. The bile duct

was not opened during surgery. Ultrasound findings were mentioned on the request form but ultrasound films/reports were unavailable. There was no mention of any metastatic disease, and it is our opinion that no metastatic investigation was performed since the surgeon was not suspicious of malignancy. The wall was diffusely thickened with a solid white cut surface. It measured 0.8 cm in maximum thickness. No discrete mass was identified. No stones were identified either in the lumen or lying separately in the container. The serosal surface was brownish with evidence of haemorrhage. The mucosa appeared ulcerated. Representative sections were taken including a section from the resection margin. Microscopic examination revealed sheets of signet ring cells infiltrating the full thickness of the wall (figures 1 and 2A). The signet ring cells comprised over 90% of the tumour cells. In a few areas small clusters of tumour cells were also seen. The surface epithelium showed evidence of dysplasia. On special stains (periodic acid–Schiff (PAS) ± Alcian blue (AB)), the signet ring cells were seen to contain acid mucin in their lumina (figure 2B). Immunohistochemical stain cytokeratin AE1/AE3 was positive in the tumour cells (figure 2C). Tumour cells were negative for caudal type homeobox 2 (CDX2) (figure 3) and were positive for cytokeratin 7 (CK7) (figure 4) and CK20 (figure 5). The gall bladder resection margin was focally involved by the tumour. The case was signed out as primary signet ring cell carcinoma of the gall bladder.

TREATMENT

The request form mentioned that an open cholecystectomy was performed for chronic cholecystitis and cholelithiasis. The specimen was received from a region of Northern Pakistan where a major military offensive against terrorists has

Figure 1 Gross picture.

been in progress for the past several months and millions of people have been displaced. We have repeatedly tried to contact the patient and the surgeon, but our efforts have so far failed.

OUTCOME AND FOLLOW-UP

No information regarding outcome and follow-up is available at this point in time due to the reasons outlined in the treatment section.

DISCUSSION

Various case reports are present in the literature describing this rare variant of gall bladder carcinoma.^{1–4} In the case report by Karabulut *et al*,¹ the patient (a 76-year-old man) died within 3 months in spite of radical surgery and chemotherapy. In our patient, there were a few areas that microscopically showed a conventional adenocarcinoma pattern. However, over 90% of the tumour was composed of sheets of signet ring cells. Additionally, grossly the gall bladder did not show a discrete mass, rather it showed a diffuse thickening of the wall resembling a linitis plastica appearance as seen in signet ring cell type gastric adenocarcinoma. This corresponds to what has been reported in the literature previously.³ Krunić *et al*⁶ reported a case of signet ring cell adenocarcinoma of gall bladder with multiple metastases to the skin in the form of nodules on the skin, scalp and perianal area. Multiple metastases to bone were also seen. These developed 1 year after resection, while no visceral metastases were detected after 20 months of follow-up. Naylor *et al*⁶ reported a case of signet ring carcinoma presenting with meningeal carcinomatosis. It was only after extensive investigation that a gall bladder primary tumour was detected. Olinici and Vasile⁷ reported a composite endocrine cell, typical and signet ring adenocarcinoma of the gall bladder. They suggested the presence of a common primitive cell with the capacity to differentiate to different types of metaplastic epithelium, which supports the hypothesis of a metaplasia–dysplasia–carcinoma sequence. Nishida *et al*⁸ reported a human gall bladder signet ring cell adenocarcinoma cell line. It must be mentioned that benign signet ring cell change, in the form of signet ring cell aggregates, sometimes occurs in the gall bladder and colonic mucosa. These may lead to multilayering of the mucosa,

Figure 2 A. Histological section showing diffuse sheets of signet ring cells infiltrating the gall bladder wall. H&E stain, magnification $\times 20$. B. Histological section showing positivity of acid mucin in cytoplasm of signet ring cells. Periodic acid–Schiff (PAS) and Alcian blue (AB), magnification $\times 40$. C. Histological section showing positivity of signet ring cells to immunohistochemical antibody cytokeratin AE1/AE3. Magnification $\times 240$.

but are always confined to the mucosa. There are never any dysplastic changes in the epithelium nor is there any invasion of the submucosa or the muscle wall. However this change is a rare and misleading diagnostic pitfall that must be kept in mind when making a diagnosis of signet ring carcinoma in gall bladder, and indeed more importantly in the

Figure 3 Caudal type homeobox (CDX)2 immunostain negative in tumour cells, $\times 20$ magnification.

Figure 4 Cytokeratin (CK)7 immunostain diffusely positive in tumour cells, $\times 20$ magnification.

Figure 5 Cytokeratin (CK)20 immunostain diffusely positive in tumour cells, $\times 20$ magnification.

colon.^{9 10} Additional histological investigations such as immunostaining with CK7, CK20 and CDX2 may be helpful in this regard. It is important to rule out entities such as carcinosarcoma and lymphangiosarcoma of the gall bladder wall. There are case reports in which these rare tumours are described.

Learning points

- ▶ Primary signet ring carcinoma is a rare histological variant of gall bladder carcinoma.
- ▶ Before diagnosis, secondary involvement of gall bladder from carcinoma of stomach or colon should be ruled out by additional histological investigation such as additional immunohistochemical staining with cytokeratin (CK)7, CK20 and Caudal type homeobox (CDX)2.
- ▶ Primary signet ring carcinoma shows surface dysplastic epithelium. Since very few cases have been reported, information regarding behaviour and prognosis is limited. It should also be mentioned that although there is still controversy about the role of surgery in patients with advanced gall bladder cancer, such patients could still benefit from an aggressive, radical and potentially complete curative resection.

Competing interests None.

Patient consent Obtained.

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