CASE REPORT

Castleman's disease in carcinoma gall bladder

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SUMMARY

Castleman's disease (CD) also known as angiofollicular lymph node hyperplasia represents a group of uncommon non-clonal lymphoproliferation. We herein report a case of CD associated with carcinoma of the gall bladder. To the best of our knowledge, it is the first of its kind and has not been reported in the past. The hypothesis regarding the aetiopathogenesis of CD is that it is associated with interleukin-6 surges. This may be explained by the overproduction of IL-6 by tumour cells or IL-6 production due to a long-standing/smouldering localised inflammatory response. An important question raised by this observation is whether the finding of CD has any effect on the outcome of this patient of carcinoma of the gall bladder. Further research is required in this matter.

BACKGROUND

The most common location for the CD is the abdomen followed by retroperitoneal, cervical, axilla, groin and pelvic lymph nodes. The incidence of the disease in the abdomen is rarely associated with biliary pathology. When found, it may be peripancreatic or mesenteric. It may be seen as mass lesions on imaging, sometimes mimicking malignant lesions.

Intraoperatively, we found that the patient had lymph node near porta hepatis, mimicking malignant lymph nodes, which turned out to be CD on histopathology. We believe that this is the first case of its kind and have not come across a similar case in any literature review.

The dilemma of managing cases with such findings and its impact on prognosis is unknown; hence, we are reporting our experience in the pool.

CASE PRESENTATION

An HIV-negative woman aged 54 years presented to our department with a history of pain in the right upper abdominal quadrant for around 3 days. She also gave a history of fever with nausea since the last 2 days. An ultrasonogram of her abdomen revealed multiple gallbladder stones with stones in the common bile duct (CBD). There was mild intrahepatic biliary radical dilation. She had an elevated leucocyte count (16 000/mm³), total bilirubin (3.6 mg/dL) and deranged liver enzymes (alkaline phosphatase 545 IU, aspartate transaminase 210 IU and alanine transaminase 110 IU). A diagnosis of cholangitis with choledocholithiasis and cholecystolithiasis was made. After appropriate resuscitation, she underwent ERCP clearance of the CBD with stenting followed by laparoscopic cholecystectomy relatively which was uneventful. The patient responded well to surgery and was discharged with

advice regarding follow-up and stent removal at a later date. Histopathology analysis of the surgical specimen revealed a focus of adenocarcinoma in the wall of the gall bladder. Tumour cells had infiltrated the perimuscular tissue and cystic lymph node of Lund. The patient was staged as pT2N1 or stage IIIB. An extensive workup was performed to detect metastases. Cross-sectional imaging (as well as PET-CT) did not demonstrate active disease or suspicious lesions. A radical cholecystectomy was planned and performed. At initial exploration, no lesions or masses were found within the abdomen or the pelvis. Omental adhesions over the gall bladder fossa were excised en bloc and a complete lymphadenectomy (up to the coeliac trunk) along with subsegmental hepatic resection was performed. Analysis of the specimen did not show any residual disease (R-0 resection), but a single lymph node (at the porta along the CBD) showed changes consistent with CD. All other lymph nodes in the specimen were free of disease. We reviewed the patient's imaging again, but it failed to show any lymph node enlargement. A repeat clinical examination did not show any cervical, axillary or inguinal lymph node enlargement. A repeat HIV testing performed was reported negative. Owing to the HIV-negative status, unicentric nature of disease and the prohibitive cost (which the patient could not afford) Human Herpes virus type 8 (HHV-8) testing was not performed. The patient had an uneventful recovery and was doing well at the last follow-up. The patient preferred observation with close follow-up compared with gemcitabine therapy after being offered both the options in accordance to prevalent guidelines.

INVESTIGATIONS

Histopathology of the lymph node shows lymphoproliferation and onion ring appearance.

Rest of the liver margin and other lymph nodes were normal (figure 1).

DIFFERENTIAL DIAGNOSIS

Lymph node metastasis from carcinoma gall bladder was suspected while operating, as the CBD node was enlarged and hard in consistency.

TREATMENT

Right Kochers' incision was used and omental adhesions over the gallbladder fossa were excised en bloc and a complete lymphadenectomy (CBD, periportal, up to the coeliac trunk) along with subsegmental hepatic resection of the gallbladder fossa was performed.

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Figure 1 Histopathology of the lymph node showing lymphoproliferation (onion ring appearance consistent with CD-hyaline vascular type).

Figure 2 Probable mechanism of lymphoproliferation.

OUTCOME AND FOLLOW-UP

The patient tolerated the procedure fairly well without any major events. The patient preferred observation with close follow-up compared with gemcitabine therapy after being offered both the options in accordance to prevalent guidelines. After 6 months of radical cholecystectomy, the patient is doing well.

DISCUSSION

Castleman's disease (CD) represents an uncommon condition of angiofollicular lymph node hyperplasia. The condition was first described by Castleman in 1956.¹ It is also called giant or angiofollicular lymph node hyperplasia, lymphoid hamartoma and is

recognised as a group of uncommon lymphoproliferative disorder. It has been associated with HIV as well as HHV-8 infections.^{2,3} It has been known to be associated with lymphoma, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome and Kaposi's sarcoma.⁴ The disease may be unicentric or multicentric in distribution. The diagnosis is made on histological examination of a surgical specimen. The histological subtypes include hyaline vascular variant, plasma cell variant, mixed variant and a plasmablastic variant seen in multicentric CD.⁴ The most common location for the disease is the mediastinum followed by cervical, pelvic, retroperitoneal and axillary lymph nodes. It may be seen as mass lesions on imaging, sometimes mimicking malignant lesions.⁵ It has rarely been reported in the porta hepatis and there has been only one report in which CD mimicked an exophytic hepatocellular carcinoma at the porta.⁶ We herein report a case of CD observed in the porta hepatis in a patient with carcinoma of the gall bladder. We believe that this is the first case of its kind and have not come across a similar case in an extensive literature review. The actual mechanism by which lymphatic tissue undergoes angiofollicular hyperplasia observed in CD is yet to be conclusively proven. A leading hypothesis suggests that a surge in interleukin-6 (IL-6, local or systemic) is responsible for this non-clonal lymphoproliferation.⁷ The role of HHV-8 in HIV-positive patients may be testimony to the fact as the viral genome is a homologue for the IL-6 gene. This hypothesis holds true and explains the multicentric variant in HIV-positive patients. However, the aetiopathogenesis of the unicentric localised variant in HIV-negative patients may not be due to HHV-8 infection. It may be due to ectopic cytokine secretion by benign/malignant tumour into the lymph node/extranodal tissue (paraneoplastic syndrome hypothesis) (figure 2). There may also be a role of local inflammation that may give rise to a local surge in IL-6.⁸ Local lymph node groups may actually be the filters preventing this IL-6 surge from overflowing into the systemic circulation. Another explanation may be that the systemic effects may not be seen due to dilution or metabolism of locally produced IL-6. Therefore, the effects may be restricted to single lymph node groups.

We suspect in the case reported above, the changes suggestive of CD in a single lymph node could be due to one of the two reasons. First, it may have been due to the adenocarcinoma cells producing IL-6, which acted on the CBD lymph node (a paraneoplastic syndrome). This may have led to non-clonal lymphoproliferation resulting in CD. Second, a low-grade local inflammatory response due to a long-standing/smouldering cholecystitis/cholangitis may have caused a local surge in IL-6 leading to CD (in a local lymph node). This surge may have been appropriate only for changes of CD in the local node, therefore the unicentric nature of CD. This is probably one of the first cases to report CD associated with carcinoma of the gall bladder. Even though it may be possible to hypothesise regarding the aetiopathogenesis of CD in this case, the clinical significance of this observation is not completely understood. If indeed the CD was due to cancer, a challenging question that remains to be answered is how does this finding influence outcome? The patient had a stage IIIB (pT2N1) carcinoma of the gall bladder. We do not know how this finding influences survival or changes the prognosis. If indeed it were a paraneoplastic syndrome, it may be difficult to extrapolate it to assess tumour biology. On the one hand, it may mean severe DNA damage/rearrangement, which may suggest an aggressive tumour. On the other hand, the temporal relation between local surges of IL-6 and development of CD could mean a

slow-growing tumour with a not so aggressive biology. The patient was alive and well at last follow-up (6 months postsurgery) with no evidence of recurrence or residual disease.

Learning points

- ▶ Careful examination of lymph node histology is mandatory not just for staging of the disease but also to rule out any other disease causing lymphoproliferation.
- ▶ Immunohistochemical analysis viz CD3, CD5, CD10, CD20, CD23, CD79 and Ki-67 forms a major part of diagnosing the lymphoproliferation process (which we did not do due to financial constraints of the patients and limitations of our institute).
- ▶ Reporting of such cases is important for prognosticating the disease.
- ▶ Future research may be able to delineate the significance and how clinicians may be able to interpret this finding.

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Contributors VWD designed the article, procured details of case, formulated the figures in this article and outlined the hypothesis based on existing literature. AJN

contributed in drafting and making necessary additions in discussion and verification of the articles. SN had finalised the draft and made appropriate corrections in the final article.

Competing interests None declared.

Patient consent Obtained.

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