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Diffuse large B-cell lymphoma of the gallbladder arised 8 years after malignant lymphoma of the right testis: A case report and literature review

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ABSTRACT

INTRODUCTION: Gallbladder involvement in lymphoma is extremely rare, and only 68 cases have been reported in the English literature so far. We experienced a case of diffuse large B-cell lymphoma (DLBCL) of the gallbladder arising 8 years after DLBCL of the right testis.

PRESENTATION OF CASE: A 68-year-old man underwent orchiectomy for malignant lymphoma of the right testis pathologically diagnosed as DLBCL 8 years ago. Systemic surveillance incidentally revealed a gallbladder tumour, and elective resection of the gallbladder bed of the liver was performed under a preoperative diagnosis of gallbladder cancer. The histopathological examination revealed DLBCL. At re-evaluation 3 months after surgery, he was diagnosed as having DLBCL involving the stomach. There had been no recurrence for 39 months after chemotherapy and radiation, but he suffered from a poor general condition due to protein-losing enteropathy and died of infection.

DISCUSSION: We compiled and analysed reported cases of malignant lymphomas involving the gallbladder in terms of background, symptoms, imaging findings, and prognosis. Compared to MALT lymphoma, DLBCL was significantly more involved in other organs simultaneously or heterochronously ($p = 0.004$).

CONCLUSION: Gallbladder lymphoma should be added to the differential diagnosis of gallbladder tumours, especially when clinical findings are not consistent with the typical course of gallbladder carcinoma and cholecystitis.

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Abbreviations: CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; ERCP, endoscopic retrograde cholangiopancreatography; FDG-PET, fuluorodeoxyglucose positron emission tomography; HE, haematoxylin and eosin; IVLBCL, intravascular large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; sIL-2R, soluble interleukin-2 receptor; US, ultrasonography.

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1. Introduction

Malignant lymphomas are considered tumours of the lymph nodes, but 40% occur in extra-nodal tissues [1], usually from the gastrointestinal tract. The stomach is most often involved, followed by the small intestine, colon, and oesophagus. Gallbladder involvement by lymphoma is extremely rare, and only 68 cases have been reported in the English literature so far. We experienced a case of diffuse large B-cell lymphoma (DLBCL) of the gallbladder arising 8 years after DLBCL of the right testis. In this report, we describe the clinical course and review the clinical features of malignant lymphoma of the gallbladder as reported in the previous literature. The presented case has been reported in line with the SCARE criteria [2].

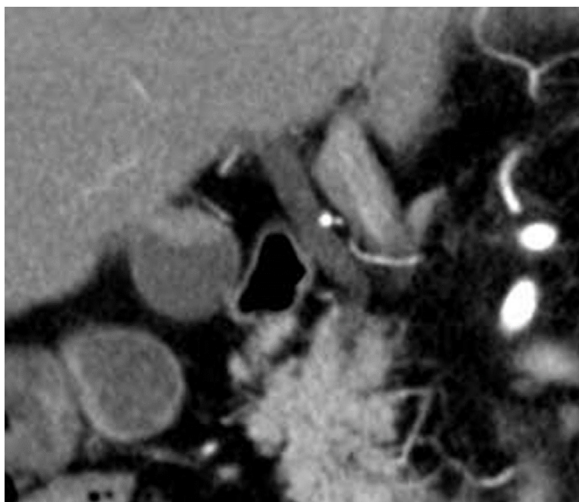


Fig. 1. Computed tomography revealed a localized mass that did not appear to invade the liver and swollen lymph nodes around the gallbladder.

2. Presentation of case

A 68-year-old man underwent orchiectomy for malignant lymphoma of the right testis, which was diagnosed pathologically as DLBCL 8 years ago. He was determined to be in complete remission following postoperative chemotherapy and radiation. Three years ago, he started to take steroids for a diagnosis of protein-losing enteropathy but suffered from avascular necrosis of the femur head due to long-term steroid use. When he was admitted to hospital to introduce immunosuppressive therapy instead of steroid therapy, systemic surveillance incidentally revealed a gallbladder tumour. He was admitted to our surgical department for investigation and elective surgery of the gallbladder lesion.

On physical examination, he had no abdominal symptoms including Murphy's sign but did have lower leg oedema reflecting hypoproteinaemia due to the protein-losing enteropathy. Laboratory findings showed moderate elevation of tumour markers CEA (5.7 ng/mL) and CA19-9 (55.7 U/mL), but his alpha-fetoprotein level was within normal limits. Serum soluble interleukin-2 receptor (sIL-2R) was slightly high at 625 U/mL (normal range, 145–519 U/mL). He suffered from chronic hepatitis B – his indocyanine green 15-min retention test result was 15.5% – that was classified as Child-Pugh class B. Abdominal ultrasonography (US) showed

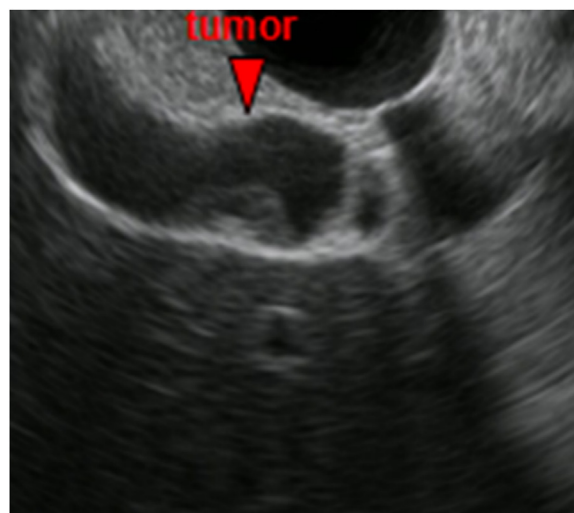


Fig. 3. Endoscopic ultrasonography showed a hypoechoic trapezoidal-shaped protruding lesion of 25 × 12 mm in size. The thickened outer hyperechoic layer was preserved, which suggested no invasion to the liver parenchyma.

a 27 × 10 mm localized, homogeneously hypoechoic mass at the gallbladder neck and body on the liver bed side. Computed tomography (CT) confirmed the same mass, which did not appear to invade the liver, and swollen lymph nodes around gallbladder (Fig. 1). Magnetic resonance imaging depicted the gallbladder lesion with low intensity on T1-weighted images and high intensity on T2-weighted images compared with the intensity in the liver parenchyma (Fig. 2a, b). ¹⁸F-Fluorodeoxyglucose positron emission tomography (FDG-PET) confirmed these findings (maximum standardized uptake value = 6.9) with no evidence of malignancy in other organs. Endoscopic retrograde cholangiopancreatography (ERCP) revealed lateral deformation with an irregular surface at the neck and body of the gallbladder. Cytology of the bile juice obtained from the common bile duct resulted in a Class I designation. Endoscopic ultrasonography showed a hypoechoic trapezoidal-shaped protruding lesion of 25 × 12 mm in size. The thickened outer hyperechoic layer was preserved, which suggested no invasion of the liver parenchyma (Fig. 3).

After discussion and review of the findings, including focal uptake on FDG-PET imaging, in our surgical team meeting, an elective resection of the gallbladder bed of the liver and D1 lymph node dissection was performed under the preoperative diagnosis

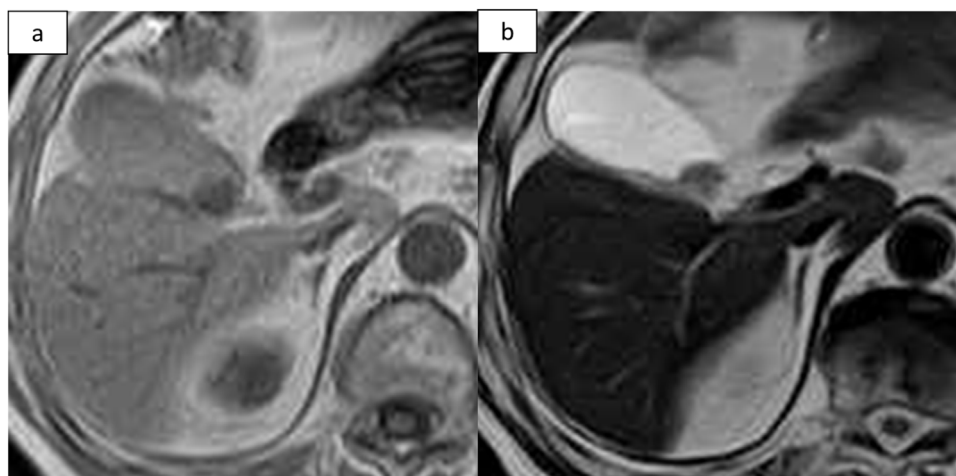


Fig. 2. Magnetic resonance imaging of the gallbladder lesion showed low intensity on a T1-weighted image (a) and high intensity on a T2-weighted image (b) compared with the intensities of the liver parenchyma.

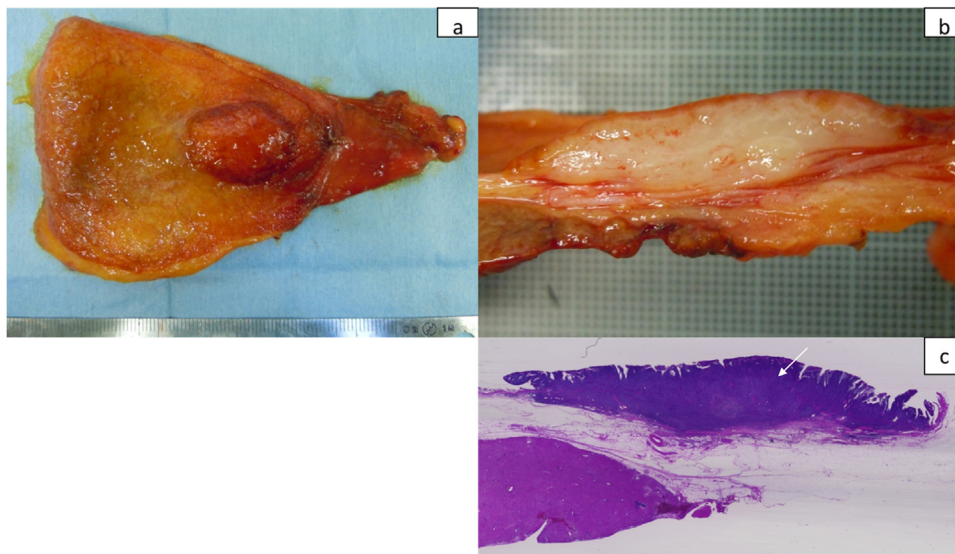


Fig. 4. The resected specimen showed a submucosal tumour-like lesion of 28 × 15 mm in size (a). Split image of the tumour showed an expanding appearance and homogenous white colour (b). Haematoxylin and eosin staining showed lymphocytes mainly in the mucosal layer with muscular and subserosal propria invasion (arrow) (c).

of gallbladder cancer (Gnb, nodular type with infiltrating growth pattern, 25 × 12 mm, SS, Hinf1a, H0, Binf0, PV0, A0, P0, M0, cStage II). The resected specimen (Fig. 4a, b) presented a submucosal tumour-like lesion of 28 × 15 mm in size at the neck and body of the gallbladder on the liver bed side. The split image of the tumour showed an expanding appearance and homogenous white colour. Histopathologically, hematoxylin and eosin staining showed diffuse infiltration of atypical large-sized lymphocytes mainly in the mucosal layer with muscular and subserosal propria invasion (Fig. 4c). The gallbladder itself showed histological evidence of cholecystolithiasis and cholesterolosis. Immunohistochemical examination revealed the infiltrated lymphocytes to be CD20 and CD79a positive, and CD3e negative, which was similar to the pattern of histological findings of specimen of the right testis resected 8 years ago (Fig. 5a–h). In addition, CD10-negative and BCL-6- and MUM-1-positive DLBCL of the non-germinal centre type was identified with gallbladder involvement.

The patient was discharged home on postoperative day 17 without any complications. At re-evaluation 3 months after surgery, the patient was diagnosed as having DLBCL involving the stomach based on abnormal uptake in the gastric corpus on FDG-PET and pathological findings from a biopsy obtained by gastroscopy. There had been no recurrence for 39 months after chemotherapy and radiation, but he suffered from a poor general condition due to the protein-losing enteropathy and died of infection.

3. Discussion

Malignant lymphoma of the gallbladder is extremely rare. Among the malignant tumours of the gallbladder, 98% are adenocarcinomas and only 0.1–0.2% are lymphomas [3–5]. From our search of the literature on PubMed from 1985 to 2020, only 68 cases of malignant lymphomas involving the gallbladder have been reported that described the clinical course in detail. We list these reports in terms of background, symptoms, imaging findings, and prognosis in Table 1.

The average age of onset was 65.6 years old, and the rate of occurrence tended to be slightly higher in males than females. Some symptoms were associated with cholecystitis such as fever and abdominal pain, and lymphoma symptoms such as weight loss and night sweats were observed, but some cases were asymptomatic and accidentally revealed by diagnostic imaging as in our case. As

Table 1

Detailed clinical features of 68 reported cases of malignant lymphoma of the gallbladder.

| | |
|-------------------------|----------------------------|
| Age (average, y/o) | 65.6 (4–88) |
| Sex (M/F) | 39/26 |
| Symptom | |
| Fever | 27.9% |
| Abdominal pain | 70.6% |
| Weight loss | 14.7% |
| Asymptomatic | 17.6% |
| Laboratory data | |
| Elevated WBC | 13.2% |
| Abnormal liver function | 33.8% |
| Elevated sIL-2R | 8.8% |
| Imaging modality | |
| US | 67.6% |
| CT | 66.1% |
| MRI | 22.1% |
| EUS | 4.4% |
| Gallstones | 38.2% |
| Operated case | 92.6% |
| Histological type | |
| MALT | 13 cases |
| DLBCL | 15 cases |
| IVLBCL | 10 cases |
| FL | 7 cases |
| Other/Not described | 23 cases |
| Involves other organ | 42.6% |
| Prognosis | |
| Described | 47 cases |
| Alive | 41.2% (2 months–8.5 years) |
| Dead | 27.9% (2 days–7 months) |

WBC: white blood cells, sIL-2R: soluble interleukin-2 receptor, US: ultrasonography, CT: computed tomography, MRI: magnetic resonance imaging, EUS: endoscopic ultrasonography, MALT: mucosa associated lymphoid tissue, DLBCL: diffuse large B-cell lymphoma, IVLBCL: intravascular large B-cell lymphoma, FL: follicular lymphoma.

many of the cases were diagnosed by pathological examination after cholecystectomy in patients with cholecystitis, the laboratory data showed elevated white blood cell counts and abnormal liver function. In contrast, in the cases in which malignant lymphoma was identified as a differential diagnosis preoperatively, there were several reports of elevated sIL-2R levels. US and CT were performed in many cases and, showed various imaging findings such as tumours and polyps, and focal or diffuse wall thickening was observed. Yokoe et al. suggested that findings on US revealed

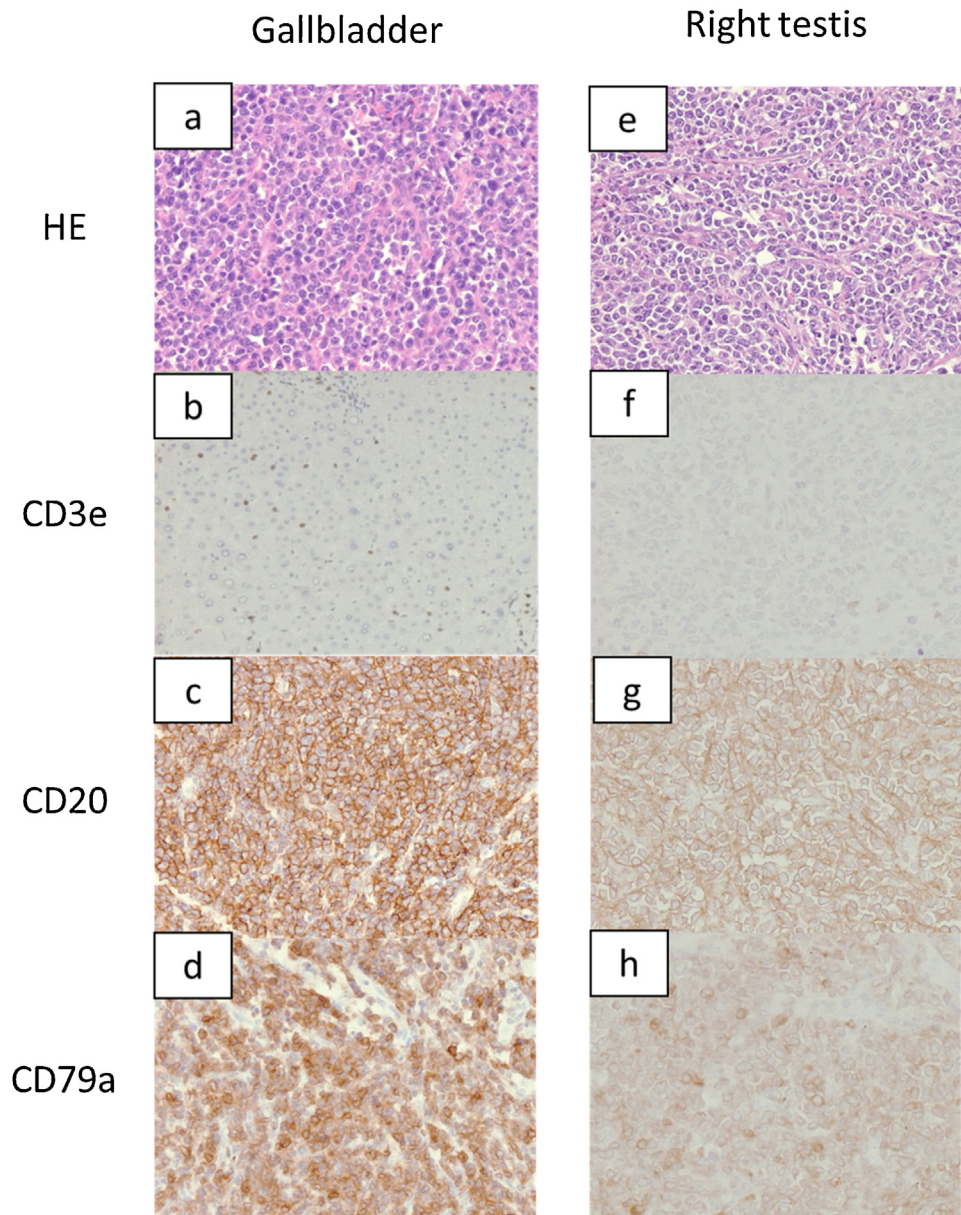


Fig. 5. Haematoxylin and eosin (HE) staining showed atypical large-sized lymphocytes (a). Immunohistochemical examination revealed the infiltrated lymphocytes to be CD3e negative (b) and CD20 (c) and CD79a (d) positive, which was similar to the pattern of histological findings of the specimen of right testis resected 8 years ago (e–h).

the internal lower echoic level of the tumour in comparison to gallbladder carcinoma, although no special findings were found in a CT study [6].

Few patients have been accurately diagnosed preoperatively, and many patients have undergone surgery under a diagnosis of gallbladder carcinoma, cholecystitis, or symptomatic cholelithiasis. Kuramitsu et al. reported a rare case of gallbladder intravascular large B-cell lymphoma (IVLBCL) postoperatively after liver transplantation for acute liver failure [7]. There was also a case in which systemic chemotherapy was performed without surgery due to a diagnosis based on bile cytology obtained with ERCP [8].

The histological types were frequently reported as mucosa-associated lymphoid tissue (MALT) lymphoma [9,10], DLBCL [7,11], IVLBCL [6,12] and follicular lymphoma [13,14], and there were rare cases with the coexistence of DLBCL and MALT lymphoma [15], and malignant lymphoma and gallbladder adenocarcinoma [16]. We compare the clinical features of reported cases of gallbladder MALT lymphoma (n = 13) and gallbladder DLBCL (n = 15) in Table 2 to evaluate the difference in characteristics between the two subtypes,

Table 2

Clinical features of the reported cases of MALT lymphoma and DLBCL of the gallbladder.

| | MALT lymphoma (n=13) | DLBCL (n=15) | P value |
|----------------------|----------------------|--------------|---------|
| Age (average, y/o) | 67.5 (31–88) | 60.9 (32–82) | 0.284 |
| Sex (M/F) | 5/8 | 10/4 | 0.085 |
| Gallstone | 7 cases | 4 cases | 0.141 |
| Lesion (described) | 11 cases | 13 cases | |
| Focal | 6 cases | 6 cases | |
| Diffuse | 5 cases | 7 cases | 0.142 |
| Involves other organ | 2 cases | 8 cases | 0.004 |
| Simultaneous | 1 cases | 5 cases | |
| Heterochrony | 1 cases | 3 cases | |

MALT: mucosa associated lymphoid tissue, DLBCL: diffuse large B-cell lymphoma.

which are considered to be common in gastrointestinal malignant lymphoma, including the stomach. Statistical evaluation was performed using StatFlex version 7, and $p < 0.05$ was considered to indicate statistical significance. Significant findings were associated

with the simultaneous or heterochronous involvement of other organs ($p = 0.004$). They tended to be gallstones in the MALT lymphoma group ($p = 0.141$), although no significant difference was observed. The gallbladder is generally considered to be an organ that does not have lymphoid tissue [17], and there is controversy about the cause of extranodal malignant lymphoma in the gallbladder. Mosnier et al. speculated that lymphocyte infiltration into the gallbladder wall due to chronic inflammation and secondary lymphoid follicle formation are the aetiologies of malignant lymphoma of the gallbladder [18]. In fact, Tomori et al. reported that a MALT component was found in 158 of 1341 cases in cholecystectomy specimens and that the gallbladder could be a genesis of malignant lymphoma [19]. Based on the results of the above comparative data, MALT lymphoma may be triggered by some type of inflammation including gallstones, and DLBCL may be associated with the course of secondary infiltration of systemic lymphoma lesions as seen in the present case. In the reported cases of MALT lymphoma, curative resection was performed 12 of the 13 cases. Among them, postoperative adjuvant chemotherapy was not administered in 4 cases in which the postoperative course was described in detail, and no recurrence was observed in any of these cases. However, curative resection was performed in 2 of 15 DLBCL cases (4 of which were not described in detail). One patient remained recurrence-free for 42 months without postoperative adjuvant therapy, and the other underwent postoperative radiation therapy, but a recurrent tumour was observed in the retroperitoneum at postoperative month 32. Although a randomized controlled trial conducted by Avilés et al. [20] showed that adjuvant chemotherapy after curative resection for DLBCL localized in the stomach reduced the rate of recurrence, there is no clear guideline for adjuvant therapy after curative resection for malignant lymphoma of gallbladder.

In the present patient, resection of the gallbladder bed of the liver and D1 lymph node dissection were performed under a diagnosis of gallbladder cancer with possible liver bed invasion. However, in low-grade lymphomas such as MALT lymphoma or follicular lymphoma, it is possible that a cure can be expected only with cholecystectomy. Moreover, cholecystectomy as a total biopsy might be useful from the viewpoint of the smooth introduction of systemic therapy to treat high-grade lymphomas such as DLBCL or IVLBCL. From these points, it is important to consider this disease as a differential diagnosis of gallbladder tumour when malignant lymphoma is suspected due to the patient's history or symptoms.

4. Conclusions

Gallbladder lymphoma should be added to the differential diagnosis of gallbladder tumours, especially when clinical findings are not consistent with the typical course of gallbladder carcinoma and cholecystitis.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

This is not a research study.

Consent

Because the patient died, the authors were not able to acquire an agreement for publication.

Author contribution

Kengo Kai wrote the case report. Takeomi Hamada, Masahide Hiyoshi, Naoya Imamura, Koichi Yano, Motoaki Nagano, Masahiro Kai, Tomonori Hidaka, Kazuya Shimoda, Yukihiko Haruyama, and Hiroaki Kataoka performed the literature review and clinical assessment; Atsushi Nanashima approved the final version of the manuscript.

Registration of research studies

N/A.

Guarantor

This is not a research study. All authors read and approved the final manuscript. Therefore, all authors are responsible for this article.

Provenance and peer review

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