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CASE REPORT

Pancoast syndrome due to pulmonary metastasis of sarcomatoid hepatocellular carcinoma

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Abstract

Introduction: Hepatocellular carcinoma is the most common primary liver malignancy, and sarcomatoid hepatocellular carcinoma is a rare malignancy containing both carcinomatous and sarcomatous components. *Case Report:* We report a 64-year-old male patient treated with open right trisectionectomy for a 16cm right hemiliver tumour. The diagnosis of sarcomatoid hepatocellular carcinoma was confirmed on histology. Five months after hepatic resection, patient had symptoms suggestive of Horner's syndrome along with left sided shoulder pain, hand weakness, reduced power of the intrinsic hand muscles and reduced pain perception over the C8/T1 dermatome. Magnetic Resonance Imaging (MRI) showed a mass at the left lung apex/superior sulcus involving the left C8, T1 nerve roots, scalene muscles, and brachial plexus. The mass closely abutted the left first rib and partially encased the left subclavian artery. The patient was managed with palliative chemoradiotherapy for Pancoast syndrome. *Discussion:* Hepatocellular carcinoma pulmonary metastasis causing Pancoast syndrome is a rare occurrence with only four prior reports, and to the best of our knowledge, pulmonary metastasis from sarcomatoid hepatocellular carcinoma causing Pancoast syndrome is unreported. In this report, we will discuss the clinicopathological characteristics of this case which may provide insight into diagnosis and management of other sarcomatoid hepatocellular carcinoma patients.

Keywords: Hepatectomy, Pancoast syndrome, sarcoma

INTRODUCTION

Primary liver cancer is the fifth most common prevalent cancer and the third commonest cause of cancer-attributed mortality.[1] Hepatocellular carcinoma (HCC) is the principal histological type of liver cancer and accounts for about 75% of liver cancers.[2] Sarcomatoid hepatocellular carcinoma (SHC) is a rare form of HCC comprising of epithelial cells and mesenchymal spindle cells which makes up for about 1.8-3.9% of HCC cases.[3] The most common site of metastasis for HCC is the lung[4], and SHC metastasis to the lung is also reported.[5] Despite the prevalence of liver cancer metastasis to the lung, according to our research there are only four Pancoast syndrome reports from primary HCC related pulmonary metastases, and none from SHC.[6-9] In this case report, a patient with known history of SHC presented with symptoms of Pancoast Syndrome due to pulmonary metastasis of SHC 5 months after hepatic resection. The case highlights the rare possibility of SHC pulmonary metastasis to cause Pancoast Syndrome which may provide insight into diagnosis and management of other SHC patients.

CASE REPORT

A 64-year-old man with 50 pack-years smoking history was referred for loss of weight (two months), loss of appetite with early satiety (two weeks), and upper abdominal growth/lump. He reported night sweats, dark urine and was febrile. His history included benign prostatic hyperplasia and erectile dysfunction. His elder brother had liver malignancy. Physical examination showed pallor, hepatomegaly, and temporal wasting. Laboratory investigations showed normal thyroid and renal function, elevated alkaline phosphatase (ALP) of 606 U/L, elevated gamma-glutamyl transferase (GGT) of 417 U/L, normal bilirubin of 21 μmol/L, prolonged

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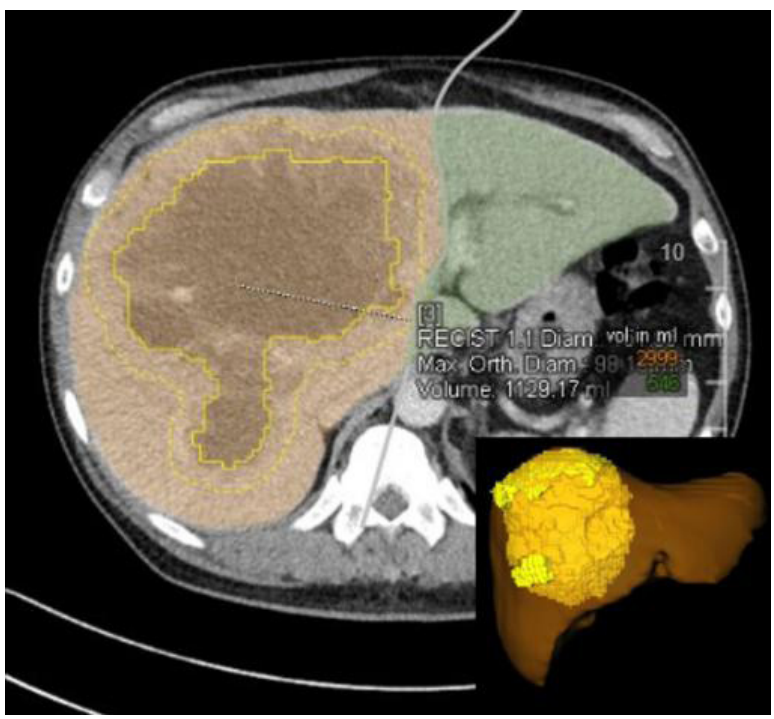
activated partial thromboplastin time of 49.8s, normal prothrombin time of 15.7s, haemoglobin (Hb) of 8.2g/dL, serum iron 3 μmol/L (normal range is 10-30 μmol/L), ferritin 1339 μg/L (normal range 24-336 μg/L), transferrin 1.5g/L (normal range 2-3.6g/L), and iron saturation 8% (normal 15-45%). Serum fibrinogen was 9g/L (normal range 1.8-4.5g/L). Dengue serology, human immunodeficiency virus serology, Hepatitis B surface antigen and anti-Hepatitis C antibody were negative, but anti-Hepatitis B core antibody total was positive, possibly suggestive past hepatitis B infection. Serum tumour markers including alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen were normal. A computerised tomography (CT) scan of thorax, abdomen and pelvis showed a 16cm right hemi-liver mass (Figure 1). Gastroscopy and colonoscopy showed acute gastritis and right colonic diverticulosis. Blood and urine culture were negative twice and chest X-ray was normal. In view of elevated ALP and GGT, negative cultures, and persistent unexplained pyrexia, an endoscopic biliary stenting was performed, to treat possible cholangitis due to biliary obstruction secondary to large liver tumour.

FIG. 1: Computerised tomography volumetry scan showing a super-giant tumour in right hemi-liver, resection plane for right trisectionectomy, and volumetry. The inset shows the tumour to liver volume ratio. The standardised liver volume based on 62.0 kg body weight was 1047.0 ml. The volumes of segments 1, 2, 3 were 546.0 ml. Thus, residual liver volume to standardised liver volume ratio was 52.1%.

The multidisciplinary team recommended liver resection for suspected hepatocellular carcinoma (HCC), as there was no metastatic disease. The indocyanine green dye retention test showed 27.9% retention at 15 minutes, making him unsuitable for major liver resection based on conventional criteria using 15% cut-off. However, due to adequate future liver remnant volume and judgment that majority of the resected liver parenchyma was non-functional, a balanced decision was made to proceed with liver resection. The patient underwent an open right trisectionectomy, and post-operative course was uneventful. Histopathological examination revealed a pT2Nx poorly differentiated HCC with clear cell change and extensive areas with sarcomatoid features. The tumour showed areas of conventional HCC with macrotrabecular



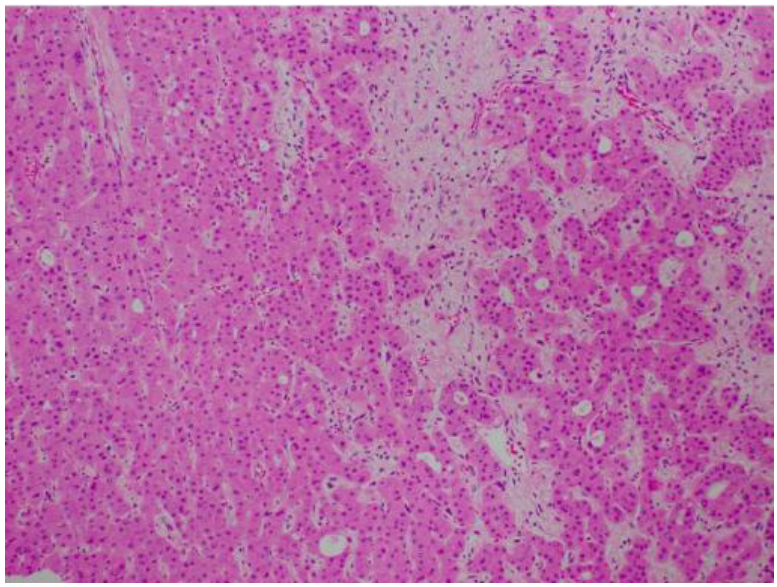


FIG. 2: Haematoxylin and eosin (H&E)-stained section of the hepatocellular carcinoma with trabecular and pseudoacinar growth patterns (x100).

and pseudoacinar growth patterns (about 35%) (Figure 2), areas where the neoplastic hepatocytes exhibited clear cell change (about 15%) (Figure 3) and extensive areas with sarcomatoid features (about 50%).

The sarcomatoid component consisted of malignant spindle cells that merged with the areas of conventional HCC (Figure 4). Large zones of necrosis were present within the tumour. A final diagnosis of sarcomatoid hepatocellular carcinoma (SHC) was established. As the tumour was completely resected, no adjuvant therapy was advised, and active surveillance was scheduled.

The CT scan at four months from surgery showed a new hypodense lesion in segment 2 of the liver, multiple bilateral left lung metastases and left anterior chest wall metastases (Figure 5).

The patient was started on three courses of Atezolizumab + Bevacizumab systemic chemotherapy. Five months after surgery and

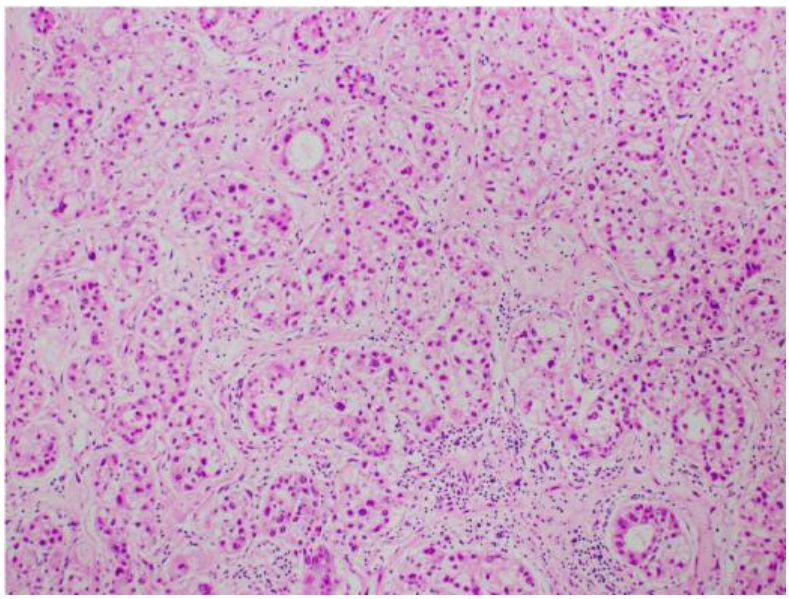


FIG. 3: H&E-stained section showing malignant hepatocytes with clear cell change (x100).

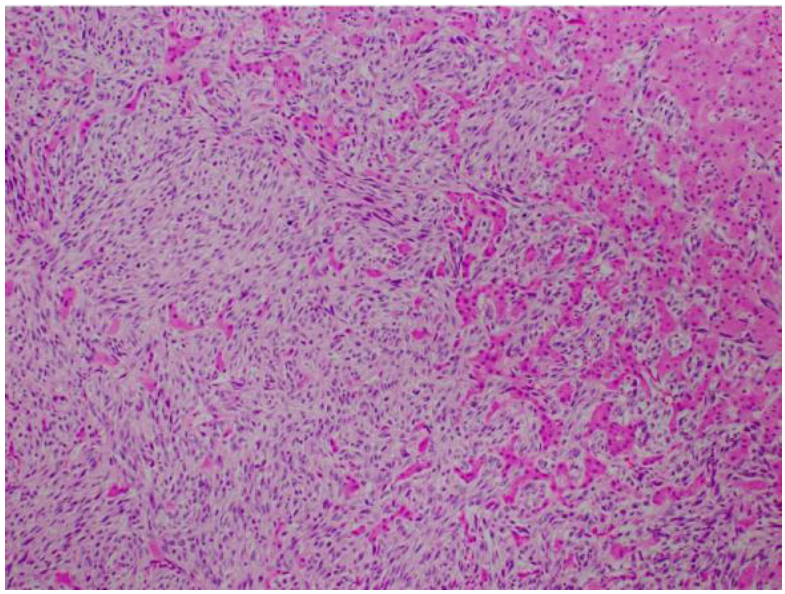


FIG. 4: H&E-stained section showing areas within the tumour where the malignant hepatocytes with ample pink cytoplasm transit into malignant spindle cells with elongated nuclei and cytologic atypia, consistent with sarcomatoid transformation (x100).

3 months after the third course of systemic therapy, he presented with left shoulder pain with numbness over the left elbow to hand of one week's duration. This was associated with left hand weakness, eye drooping, reduced power (3/5) of the intrinsic hand muscles (C8 and T1 myotomes) and reduced pain perception over the C8/T1 dermatome. Physical examination revealed a hard 12x12cm left chest wall mass with partial left ptosis. Magnetic resonance imaging (MRI) of the whole spine showed a heterogeneous mass at the left lung apex/superior sulcus involving the left C8, T1 nerve roots, scalene muscles, and brachial plexus. The mass closely abutted the left first rib and partially encased the left subclavian artery. He was started on palliative radiotherapy for Pancoast syndrome due to pulmonary metastases from SHC, with partial treatment response.

Seven months post-surgery, he presented with worsening dyspnoea secondary to pneumonia and pleural effusion from lymphangitic carcinomatosis. He also presented with fever likely due to sepsis which was complicated by acute myocardial injury. A CT-scan was performed at presentation (Figure 6). The patient demised in this presentation.

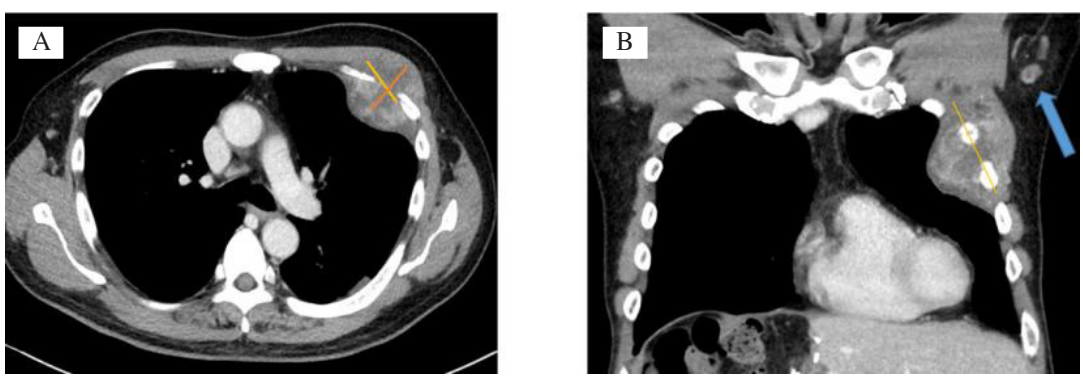


FIG. 5: Image A shows axial view of computerised tomography scan at 4 months following right trisectionectomy. This shows right chest wall metastases. Image B shows the coronal view showing left third rib erosion and left axillary lymph node metastases (blue arrow).

DISCUSSION

In this case we describe a male patient who presents with Pancoast syndrome due to pulmonary metastases from SHC. There are four prior reports of Pancoast syndrome caused by primary HCC pulmonary metastases[6-9] and none from SHC. This report adds to the existing literature on this rare pathology. Recognition and management are essential as permanent impairment of neurological function may occur if the diagnosis or management is delayed.

Sarcomatoid carcinoma is defined as a tumour containing an intimate mixture of carcinomatous and sarcomatous elements. Sarcomatoid change in HCC is defined as "sarcomatous HCC" in the World Health Organization (WHO) classification.[10] The diagnosis of SHC should be made when a sarcomatous component consisting of malignant spindle cells[11] is present within a conventional HCC. Sarcomatoid differentiation of HCC is uncommon.[12] Microscopically, there is a transition from the trabecular pattern characteristic of HCC to a sarcomatous component. The sarcomatous component consists of mainly spindle-shaped cells (spindle-cell type). Sarcomatous areas of the tumour may resemble fibrosarcoma or leiomyosarcoma with varying levels of pleomorphism with multinucleated giant cells.

SHC cases have been reported after anticancer therapy of HCC such as transcatheter arterial chemoembolisation (TACE), radiofrequency ablation (RFA), or percutaneous ethanol injection as these therapies may speed up proliferation of sarcomatous cells.[11,13] SHC is also associated with Hepatitis B and Hepatitis C infections.[14] In many instances the diagnosis of SHC is made after surgical resection, and pre-operative diagnosis by MRI and CT scan imaging lacks sensitivity.[15] In our patient, the sarcomatoid component consisted of malignant spindle cells that merged with areas of conventional HCC. Large zones of necrosis were also present within the tumour which have been previously reported.[16]

Due to the present patient presenting with night sweats, loss of weight, loss of appetite, early satiety, hepatomegaly, and a CT scan showing a large liver mass, he was pre-operatively diagnosed with malignant liver lesion. As the tumour was technically resectable, the multidisciplinary team recommended upfront resection without tissue diagnosis. This was due to the increased risk of tumour seeding, bleeding, and infection risk associated with percutaneous liver biopsy. Elevated AFP levels are associated with HCC.[17] However, our patient did not manifest elevated AFP levels. This is similar to prior reports of SHC which show a significantly

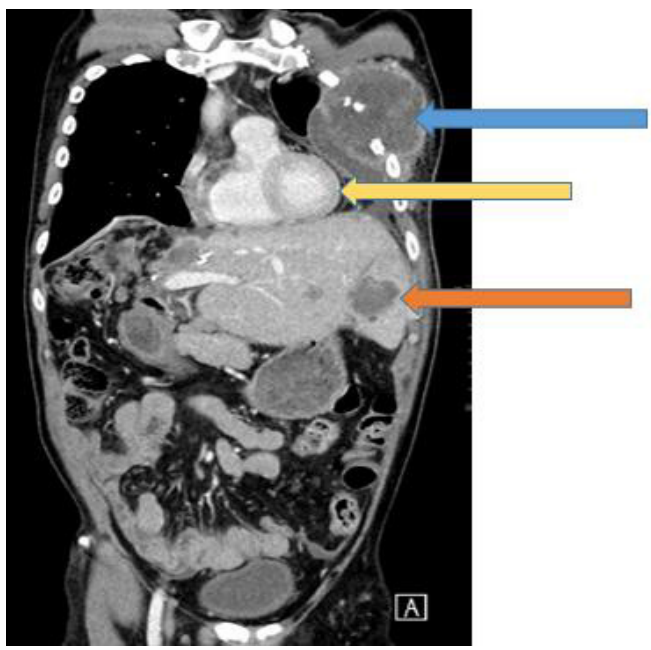


FIG. 6: The computerised tomography scan at 7 months following right trisectionectomy. This shows progression of right chest wall metastases with infiltration of left lung apex and first rib erosion (blue arrow), mediastinal lymph node enlargement (yellow arrow), and liver metastases (orange arrow).

lower positive rate of AFP in SHC compared to primary HCC.[18] In patients with normal AFP levels, serum ferritin levels may aid in diagnosis of HCC. Zhou *et al*. has reported that 38% of HCC patients have elevated ferritin, and ferritin complements AFP in diagnosis of HCC.[19] In a prospective study of hepatitis B patients, Bian *et al*. has reported that hepatitis B patients who develop HCC had significantly high ferritin level than those who remained cancer-free.[20] Furthermore, compared to patients with a ferritin level less than 200ng/ml, the patients with a high ferritin level (≥200ng/ml) had 2.43-fold increased risk of HCC (95% confidence interval 1.63-3.63). Ferritin level in our patient was four times the normal levels. The patient also did not present with elevated CA 19-9 levels. Elevated levels of CA 19-9 has been shown to be predictive of poor prognosis in both pancreatic and hepatic malignancies.[21] The normal CA 19-9 level in the present case is not in keeping with prior studies of SHC which reported elevated CA 19-9 levels in SHC patients.[22] Huang *et al*. conducted a meta-analysis to study the role of plasma fibrinogen as a prognostic marker in HCC patients. They concluded that plasma fibrinogen was a negative prognostic marker in HCC patients due to lower recurrence free survival and overall survival in HCC patients with elevated fibrinogen.[23] Our patient had elevated fibrinogen up to two times the normal limits. The poor serologic prognosticators could be due to super-giant size and indicate aggressive disease biology in SHC patients.

SHC is a post-resection histological diagnosis, and management principles are similar to primary HCC. Liver resection or liver transplantation remains the mainstay curative modalities in HCC patients. In our patient, liver transplantation was not an option due to size-based exclusion criteria. Multiple treatment modalities such as TACE, RFA or microwave ablation, systemic chemotherapy and immunotherapy are described based on disease stage, patient fitness, and liver function.[3] In our patient, the multidisciplinary team recommended liver resection as patient had preserved liver function, adequate future liver remnant, and resection would also palliate his symptoms of right upper abdominal discomfort. In general, patients with ICG retention time of more than 15% at 15-minute would be excluded from being considered for major liver resection.[24] However, in our patient, despite ICG retention of 27.9%; right trisectionectomy was performed. This was a carefully made clinical judgment based on CT liver volumetry studies as well as normal liver function serology. It is possible that the super-giant size of liver tumour contributed to defects in biliary excretion and thus could have spuriously elevated the ICG retention. We do not advocate that such exceptions should be routinely made; but instead propose that each patient should have treatment recommendations made by multidisciplinary team taking in account all necessary information and management plans should not be prescribed by fixed set of rules. In a study reporting on compliance with RIGHT checklist for reporting of clinical guidelines, Chen *et al*. has reported that reporting quality of current HCC management guidelines remain suboptimal.[25] Further, in fit and healthy patients with good performance status, it is essential that clinicians recommend curative treatment choices, and not remain restricted to guideline-based recommendations. For example, in a study including 667 HCC patients, Selby *et al*. has reported that Barcelona Clinic Liver Cancer (BCLC) stage C patients had improved clinical outcomes if they were managed according to Hong Kong Liver Cancer (HKLC) system.[26] Thus, adopting a single system to determine HCC management may deprive some HCC patients of emerging treatment options and choices that could improve survival. In our patient, despite aggressive management approach by right trisectionectomy, early recurrence happened. Early metastasis is a typical feature of SHC. Yamamoto *et al*. reported that SHC had a very high prevalence of metastasis with 70% of patients experiencing metastasis, including intrahepatic metastasis.[27] In our patient, both intrahepatic and extrahepatic metastases occurred early after resection. The pulmonary metastases progressed towards Pancoast syndrome.

Pancoast syndrome consists of atrophy of hand muscles, Horner's syndrome (ptosis, miosis and anhidrosis) and pain in the shoulder and arm following the C8, T1 and T2 nerve distributions.[28] Pancoast syndrome is caused by lung cancers at the superior pulmonary sulcus that directly spread to the inferior portion of the brachial plexus and the stellate ganglion.[29] Pancoast syndrome is commonly caused by non-small cell carcinoma, adenocarcinoma, and large cell carcinoma of the lung.[28] While there have been prior reports of HCC causing Pancoast syndrome[6-9], there have been no reported cases of SHC causing Pancoast syndrome. Due to the CT scan showing a left apical lung mass abutting the left first rib and associated symptoms on a background of

SHC, we diagnosed our patient with Pancoast syndrome due to pulmonary metastasis of SHC. Pancoast syndrome can be managed trimodally with a combination of chemoradiotherapy and surgery.[30] Due to the presence of metastases in our patient, palliative chemoradiotherapy was implemented. There was disease progression with worsening of functional status. His symptoms were managed along with palliative care team and the goals of therapy were shifted from cure towards comfort and care.

CONCLUSIONS

In conclusion, we report a patient diagnosed with primary SHC causing Pancoast syndrome due to pulmonary metastasis. While an attempt to improve survival was made by surgical resection, the disease recurred early. SHC are aggressive tumours with poor prognosis and due to paucity of literature, clinicians should report their experience. In our patient, elevated ferritin and fibrinogen were important diagnostic and prognostic adjuncts to routine HCC tumour markers.

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