superior marker to S100 in the setting of differentiation between SP and MP.

Recent studies on genetic analyses for SP and MP have shown that these two tumours are genetically different; *BRAF* or *HRAS* mutations have been detected in both SP and MP,^{7,8,10} but concurrent *AKT1* mutations are found in MP¹⁰ and are absent in SP.⁸ Indeed, *AKT1* mutations were not detected in the present case of SP. Further studies are warranted for the genetic characterisation of SP arising in unusual anatomical sites, including the bronchus.

Recently, Hsieh, *et al.* reported that SP consists of two morphologically distinct subtypes: conventional subtype and oncocyctic variant.⁷ Based on SOX10 positivity and the lack of oncocyctic change, the present case of SP would be classified as the conventional subtype. In oncocyctic SP, the ductal component is entirely lined by SOX10-negative oncocyctic cells with abundant eosinophilic cytoplasm and bland-looking nuclei.⁷ Among the constituent cells of MP, ciliated cells may occasionally show eosinophilic cytoplasm.¹⁰ Therefore, the distribution and cytomorphology of oncocyctic cells are different between MP and oncocyctic SP, although it remains unknown whether oncocyctic SP can occur in the bronchus.

We summarised a comparison of the clinicopathological characteristics between SP and MP in Table 1. These two tumours are entirely different entities in terms of their origin. The differing histological findings along with the results of SOX10 immunohistochemistry can help discriminate between SP and MP.

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Eosinophilic renal cell carcinoma with isolated *MTOR* mutation metastatic to the liver: a novel case

Sir,

Although significant advancements have been made in classifying renal cell carcinoma (RCC), approximately 5–7% of cases are still characterised as ‘unclassified’ RCCs. Studies of these ‘unclassified’ cases have shown that ~70–80% exhibit eosinophilic cytoplasm and renal oncocytoma (RO) or chromophobe RCC (CHRC) phenotypes.¹ Molecular investigations have revealed that a subset of eosinophilic renal neoplasms with heterogeneous morphology and immunohistochemical (IHC) profiles harboured mutations in the *TSC/MTOR* pathway as their primary molecular alteration.^{2–6} The metastatic potential of these neoplasms is still unknown and will require further identification of more cases and follow-up. Chen *et al.* identified two cases of *MTOR*-mutated RCCs that were both organ confined.³ In our previous study, we identified two cases of *MTOR*-mutated RCCs that were also both organ confined.⁵ In this article, we report the first case of a *MTOR*-mutated RCC that metastasised to the liver.

A 65-year-old male presented for consultation after having been diagnosed with metastatic RCC at an outside hospital. He had initially presented with low volume metastatic disease to the liver and lung and underwent a left radical nephrectomy that demonstrated an 8.5 cm renal mass. The lesion was diagnosed as unclassified RCC, Fuhrman grade 4 at the outside hospital. Following surgery, he was first treated with sunitinib with stable disease followed by nivolumab, which led to a partial response. Axitinib was then started followed by hepatic arterial yttrium-90 microspheres for persistent liver only disease. His treatment course was complicated by shortness of breath after which he was diagnosed with immunotherapy related pneumonitis.

We received the consult slides from the original radical nephrectomy, which demonstrated an 8.5×5.6×5.5 cm well-circumscribed lesion with extensive haemorrhage, necrosis, and calcifications (Fig. 1A). The tumour invaded into the renal sinus and perinephric adipose tissue, but the margins of resection (soft tissue, ureter, renal artery, and renal vein) were

Fig. 1 (A) The tumour is composed of nests of eosinophilic cells with geographic areas of necrosis and calcifications. (B) The tumour cells with eosinophilic cytoplasm merge with smaller cells containing scant amphophilic cytoplasm around (C) a hypocellular scar-like stroma. (D) There are focal areas of chromophobe-like morphology with prominent cell membranes and occasional perinuclear clearing. The nuclei are of variable size with prominent nucleoli, and rare mitotic figures are present. (E) Areas similar to RO adjacent to cells with abundant eosinophilic and vacuolated cytoplasm. (F) The 'higher grade' cells resemble the ones seen in eosinophilic solid and cystic renal cell carcinoma containing 'blue granules'.

negative. Additionally, there was metastatic RCC in one lymph node, and the patient was staged as pT3aN1. Morphologically, there were neoplastic cells with eosinophilic cytoplasm merging with smaller cells containing scant amphophilic cytoplasm (Fig. 1B). Occasionally, small nests of cells were embedded in hypocellular stroma reminiscent of a 'central scar' (Fig. 1C). Other areas resembled CHRCC with cells containing abundant clear or eosinophilic cytoplasm and prominent cell membranes with occasionally somewhat rhabdoid appearance (Fig. 1D). However, unlike the nuclei of CHRCC, the nuclei in this lesion had prominent nucleoli and rarely showed wrinkled nuclear membranes. The tumour focally showed morphology that overlapped with previously described *TSC/MTOR*-mutated renal neoplasms that had cytoplasmic vacuoles and calcifications (Fig. 1E). Lastly, the tumour had areas that mimicked eosinophilic solid and cystic RCC with cells having abundant eosinophilic cytoplasm with 'blue granules' (Fig. 1F).

IHC stains demonstrated that the tumour was negative for vimentin (Fig. 2A); focal and non-specific staining of

cytoplasmic vacuoles for CK7 (Fig. 2B); cytoplasmic staining with membranous accentuation for CD117 (Fig. 2C); and focal membranous staining for E-cadherin (Fig. 2D). P504S (Fig. 2E) and SDHB (Fig. 2F) were diffusely positive. The tumour cells were negative for CD10, vimentin, Melan-A, and TFE3. Based on the morphology rather than the IHC profile, this neoplasm was originally diagnosed at our institution as CHRCC.

A representative formalin fixed, paraffin embedded block of tissue from the original radical nephrectomy specimen was chosen for next generation sequencing on the University of Chicago Medicine OncoPlus (UCM-OncoPlus) panel, a hybrid capture panel that targets cancer associated genes. DNA extraction and quantification, library preparation, next generation sequencing, and data analysis were performed as described previously.⁵ A pathogenic mutation was identified in *MTOR* (c.7279_7280delinsAA, p.L2427K) resulting in a leucine to lysine substitution at amino acid 2427 of the protein. Codon p.L2427 has been demonstrated to be a minor hotspot mutation site in the MTOR kinase domain.⁷ Data

Fig. 2 Immunohistochemical stains for (A) vimentin, (B) CK7, (C) CD117, (D) E-cadherin, (E) P504S, and (F) SDHB.

from the Catalogue of Somatic Mutations in Cancer (COSMIC; <http://www.cancer.sanger.ac.uk/cosmic>) have identified c.7280T>A (p.L2427Q) as a somatic mutation in RCC, glioblastoma multiforme, endometrioid adenocarcinoma, and lung adenocarcinoma. Copy number variant analysis demonstrated a loss of chromosome 1 in this case.

We report the first case of an unclassified eosinophilic RCC with an *MTOR* mutation (c.7279_7280delinsAA, p.L2427K) as the primary defining mutation that was metastatic to the liver. There is increasing evidence that a subset of unclassified eosinophilic RCCs harbour mutations in the *TSC/MTOR* pathway.^{2–5} Thus far, most studies have demonstrated that these lesions appear to have an indolent course with rare metastases. In our previous study, we identified 18 cases of eosinophilic renal neoplasms with mutations in *TSC1*, *TSC2*, or *MTOR*.⁵ Of these cases, only one case had metastasis to a regional lymph node. The remaining patients were still alive at the time of analysis and had no evidence of additional disease. Chen *et al.* identified five cases that had *TSC2* or *MTOR* mutations; the patients in this cohort all had organ confined disease.³ Another study by Palsgrove *et al.* found one case of liver metastasis in a patient who previously had an eosinophilic solid and cystic RCC resected with a mutation in *TSC2*.⁴ Li *et al.* re-evaluated 33

‘unclassified’ eosinophilic RCCs and identified one case of eosinophilic solid and cystic RCC that had a metastatic focus in the hilar lymph node.⁸ A follow-up commentary to this study by McKenney *et al.* mentioned that of approximately 60 known cases of sporadic eosinophilic solid and cystic RCC, only two had documented metastatic disease.⁹ Molecular investigations were not performed in these last two situations, so it is unclear if the lesions had mutations in *TSC1*, *TSC2*, or *MTOR*.

Another lesion that was on our differential diagnosis was RO. The metastatic potential of ROs has been a topic of ongoing controversy as the 2016 World Health Organization (WHO) Renal Tumour Classification defines RO as a benign epithelial tumour but there have been several case reports describing metastases, primarily to the liver.¹⁰ The lesions in these case reports were composed of round to polygonal cells with granular eosinophilic cytoplasm; the nuclei were round to ovoid with occasional prominent nucleoli; and there was no cytological atypia or mitotic figures noted. IHC studies varied for each case, but the tumour cells were consistently negative for CD10 and vimentin with variable expression of CK7 and CD117.¹⁰ One case report did perform molecular cytogenetics and sequencing on their specimen, but they only focused on *SDHB*, *SDHC*, *SDHD*, *VHL*, and *BHD* as well as

loss of heterozygosity at 3p.¹¹ Interestingly, in the study by Chen *et al.* the cases with *MTOR* mutations were found to have loss of chromosome 1, similar to our case.³ We believe that like our case, these other case reports concerning metastatic RCCs may represent *TSC/MTOR*-mutated RCCs.

This case represents the first reported case of an unclassified eosinophilic RCC with an *MTOR* mutation as the primary molecular alteration that was metastatic to the liver. Of note, the original specimen was graded as Fuhrman grade 4, which should not have been used in this case. The appropriate grading for RCC is the WHO/International Society of Urological Pathology (ISUP) system. The grading system has been validated for clear cell RCC and papillary RCC as a prognostic indicator and should be utilised for all morphotypes of RCC for descriptive purposes. The cells in our case had occasional rhabdoid appearance, and this feature is not mentioned in the Fuhrman system.¹⁰ Appropriately identifying these lesions is critical as these patients may be treated with molecular targeted therapy. For our patient, the reported molecular studies were conducted after the aforementioned therapeutic interventions, and since he has not developed progressive disease, additional systemic treatment has not been attempted. Should the patient's disease recur, treatment with temsirolimus and everolimus may be reasonable given the good reported response to mTOR inhibitors in the presence of a mutation in *TSC1*, *TSC2*, or *MTOR*.¹² The predictive value of *MTOR* mutations and response to temsirolimus or everolimus therapy is still under investigation, but identifying RCCs with isolated *TSC/MTOR* pathway mutations may still be helpful in guiding patient therapy and management.

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Steroid-refractory T-cell mediated rejection after human metapneumovirus infection in a liver transplant recipient

Sir,

Human metapneumovirus (HMPV) is a respiratory RNA virus first described in 2001.^{1,2} HMPV is associated with T-cell mediated rejection (TCMR) in lung transplantation,³ but has not been reported in liver transplant (LT) recipients. We report the first case of steroid-refractory TCMR in a LT recipient following HMPV infection.

A 66-year-old male underwent LT for decompensated PIZZ alpha-1 antitrypsin deficiency related cirrhosis. His pre-transplant model for end-stage liver disease (MELD) was 38 and he had moderate severity chronic obstructive pulmonary disease. The patient received a donation-after-brain death whole liver graft and induction immunosuppression with methylprednisolone and tacrolimus. He was discharged from hospital 4 weeks post-LT. He was admitted to hospital 7 weeks post-LT for dyspnoea and non-productive cough. Room air oxygen saturation was 69%, which corrected with 2 L/min of supplemental oxygen. Auscultation revealed bilateral wheeze and crackles at both lung bases. Chest computed tomography confirmed an inflammatory infiltrate and bronchial wall thickening in both lower lobes. Polymerase chain reaction of nasopharyngeal aspirate detected HMPV A RNA. There was no evidence of co-existing bacterial infection. Liver allograft function was unremarkable. The patient was treated with inhaled bronchodilators. He was discharged 10 days after admission on prednisolone 20 mg daily and tacrolimus 3 mg twice daily, with trough tacrolimus concentrations between 5–7 ng/mL.

He was re-hospitalised 10 weeks post-LT for allograft dysfunction with alanine aminotransferase 1325 U/L [normal range (NR) 10–40 U/L], aspartate transaminase 690 U/L (NR 10–35 U/L), alkaline phosphatase 246 U/L (NR 30–100 U/L), gamma glutamyl transferase 593 U/L (NR 5–50 U/L), bilirubin 36 µmol/L (NR ≤20 µmol/L) and trough tacrolimus concentration of 5.6 ng/mL. Medications were unchanged and no other risk factors for rejection were identified. Liver biopsy confirmed severe TCMR. He was treated with 1 g intravenous