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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Melissa Y. Tjota¹, Jeremy Segal¹, Walter M. Stadler², Tatjana Antic¹

¹Department of Pathology, The University of Chicago, Chicago, USA; ²Department of Hematology and Oncology, The University of Chicago, Chicago, USA

Contact: Dr Tatjana Antic.

E-mail: Tatjana.Antic@uchospitals.edu

1. Iczkowski KA, Czaja RC. Eosinophilic kidney tumors: old and new. *Arch Pathol Lab Med* 2019; 143: 1455–63.
2. Trpkov K, Abou-Ouf H, Hes O, *et al.* Eosinophilic solid and cystic renal cell carcinoma (ESC RCC): further morphologic and molecular characterization of ESC RCC as a distinct entity. *Am J Surg Pathol* 2017; 41: 1299–308.
3. Chen Y-B, Mirsadraei L, Jayakumaran G, *et al.* Somatic mutations of *TSC2* or *MTOR* characterize a morphologically distinct subset of sporadic renal cell carcinoma with eosinophilic and vacuolated cytoplasm. *Am J Surg Pathol* 2019; 43: 121–31.
4. Palsgrove D, Li Y, Pratilas C, *et al.* Eosinophilic Solid and cystic (ESC) renal cell carcinomas harbor *TSC* mutations: molecular analysis supports an expanding clinicopathologic spectrum. *Am J Surg Pathol* 2018; 42: 1166–81.
5. Tjota M, Chen H, Parilla M, *et al.* Eosinophilic renal cell tumors with a *TSC* and *MTOR* gene mutations are morphologically and immunohistochemically heterogeneous: clinicopathologic and molecular study. *Am J Surg Pathol* 2020; 44: 953–4.
6. Parilla M, Kadri S, Patil S, *et al.* Are sporadic eosinophilic solid and cystic renal cell carcinomas characterized by somatic tuberous sclerosis gene mutations? *Am J Surg Pathol* 2018; 42: 911–7.

7. Grabiner BC, Nardi V, Birsoy K, *et al.* A diverse array of cancer-associated mTOR mutations are hyperactivating and can predict rapamycin sensitivity. *Cancer Discov* 2014; 4: 554–63.
8. Li Y, Reuter VE, Matoso A, *et al.* Re-evaluation of 33 “unclassified” eosinophilic renal cell carcinomas in young patients. *Histopathology* 2018; 72: 588–600.
9. McKenney JK, Przybycin CG, Trpkov K, *et al.* Eosinophilic solid and cystic renal cell carcinomas have metastatic potential. *Histopathology* 2018; 72: 1066–7.
10. Van der Kwast T, Perez-Ordóñez B. Renal oncocytoma, yet another tumour that does not fit in the dualistic benign/malignant paradigm? *J Clin Pathol* 2007; 60: 585–6.
11. Cacciamani G, Cima L, Ficial M, *et al.* Liver metastases from renal oncocytoma with vascular extension. *Appl Immunohistochem Mol Morphol* 2019; 27: e48–53.
12. Kwiatkowski DJ, Choueiri TK, Fay AP, *et al.* Mutations in *TSC1*, *TSC2*, and *MTOR* are associated with response to rapalogs in patients with metastatic renal cell carcinoma. *Clin Cancer Res* 2016; 22: 2445–52.

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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

Fig. 1 (A) Solid arrow shows portal tract with mixed inflammatory infiltrate and spillover into the peri-portal parenchyma. Open arrow indicates degenerative changes of the bile duct. (B) Solid arrow shows hepatic venule with subendothelial lymphocytes and perivenular hepatocyte necrosis. (C) Resolution of inflammation in the portal tract but lacking interlobular bile duct. (D) Presence of minimal perivenular inflammation with focal necrosis and cannicular bile plugs (solid arrow).

methylprednisolone daily for 3 days and trough tacrolimus concentrations were maintained at 8–10 ng/mL. After 7 days, there was no improvement in allograft biochemistry and repeat liver biopsy demonstrated ongoing severe TCMR (Fig. 1A,B). Allograft dysfunction persisted after a second pulse of methylprednisolone, with serum bilirubin rising to 212 μ mol/L. Subsequently, anti-thymocyte globulin (ATG) 1.5 mg/kg was administered for 10 days. Liver biopsy after ATG demonstrated prominent cholestasis with scant bile ducts (1 bile duct in 8 portal tracts) and lytic necrosis around some central veins suggestive of early chronic rejection with some improvement in inflammation and endothelialitis (Fig. 1C,D). He was discharged 6 weeks after admission with improving allograft function on mycophenolate mofetil 1 g twice daily, tacrolimus 5 mg twice daily and prednisolone 30 mg daily. Unfortunately, the patient succumbed to fatal staphylococcal pneumonia one month after discharge.

There are sparse data on HMPV infections in LT recipients. A study of 59 solid-organ transplant recipients with HMPV infection found that 16 LT recipients were infected; however, TCMR was not examined.¹ Conversely, lung allograft dysfunction has been observed in up to 63% of LT recipients following HMPV infection and can manifest as both TCMR and chronic allograft rejection.⁴ It is postulated that HMPV may potentiate a cellular immune response to non-viral antigen;⁵ however, the mechanisms are incompletely understood as many mediators of TCMR share common pathways with viral activation and epithelial injury.^{3,5} No definitive treatment for HMPV infection exists. Ribavirin with or without intravenous immunoglobulin has been given in isolated reports.² This case highlights that HMPV infection and the associated immune response in LT recipients warrant further investigation.

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Nwe Ni Than¹, Simone Chin¹, James G. Kench^{2,3}, Geoff McCaughan^{1,3,4}, Avik Majumdar^{1,3}

¹Australian National Liver Transplant Unit, Royal Prince Alfred Hospital, University of Sydney, Sydney, NSW, Australia; ²Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, University of Sydney, Sydney, NSW, Australia; ³Central Clinical School, University of Sydney, Sydney, NSW, Australia; ⁴Liver Injury and Cancer Program, The Centenary Institute, Sydney, NSW, Australia

Contact Dr N. N. Than.

E-mail: nwenithan@gmail.com

1. Koo HJ, Lee HN, Choi SH, *et al.* Human metapneumovirus infection: pneumonia risk factors in patients with solid organ transplantation and computed tomography findings. *Transplantation* 2018; 102: 699–706.
2. Seo S, Gooley TA, Kuypers JM, *et al.* Human metapneumovirus infections following hematopoietic cell transplantation: factors associated with disease progression. *Clin Infect Dis* 2016; 63: 178–85.
3. Dosanjh A. Respiratory metapneumoviral infection without co-infection in association with acute and chronic lung allograft dysfunction. *J Inflamm Res* 2015; 8: 79–82.
4. Hopkins P, McNeil K, Kermee F, *et al.* Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. *Am J Respir Crit Care Med* 2008; 178: 876–81.
5. Céspedes PF, Palavecino CE, Kaleris AM, Bueno SM. Modulation of host immunity by the human metapneumovirus. *Clin Microbiol Rev* 2016; 29: 795–818.

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