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Title

Tumour seeding of the renal tumour biopsy tract – a histologically under-recognised feature?

Running title (50 characters)

Features of renal tumour biopsy tract seeding

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Conflicts of interest

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Renal cell carcinoma (RCC) incidence is rising, partly due to incidental detection during imaging performed for other diseases.¹ Image-guided, percutaneous renal tumour biopsy (RTB) enables histological classification of small renal masses (< 4 cm), facilitating management decisions, and confirmation of RCC in patients with disseminated disease who might benefit from systemic therapy. Modern biopsy techniques, including use of a coaxial needle, are associated with increased diagnostic yield and reduced morbidity. Current guidelines suggest RTB tract seeding by tumour to be rare.² However, there are now several case reports of this, including one with histologically confirmed local recurrence.³ We recently published a series of seven patients with histological evidence of tumour seeding of the RTB tract within the perinephric fat of the subsequent resection specimen,⁴ with the incidence in our institution being 1%. Six cases were papillary RCC (PRCC) and one was clear cell RCC (CCRCC). In all but one case, the presence of seeding resulted in upstaging of the tumour and one patient developed local recurrence at a site consistent with that of the prior biopsy tract. Subsequently, we have identified one additional case of RTB tract seeding by PRCC and one highly suspicious case (RCC unclassified with papillary features), in which there was also concurrent perinephric fat invasion away from the RTB tract site.

Recognition of our first case of seeding increased vigilance in assessing for RTB tract features within post-biopsy nephrectomy specimens. Therefore, we wish to highlight the key features that permitted detection of RTB tract seeding. In 5/9 cases (56%), the RTB site was macroscopically evident as fat necrosis, haemorrhage and fibrosis in the perinephric fat and/or haemorrhagic foci at the tumour capsular surface (**Figure 1**). In some cases, there were also macroscopic features of the previous biopsy within the tumour itself, such as focal haemorrhage or necrosis. Such areas were sampled thoroughly for microscopic assessment. Provision of details of pre-operative RTB on the accompanying specimen request form was beneficial in highlighting cases to pathologists; this is particularly important for out-of-region referral patients without local histopathology records.

Figure 1

In each of our cases, there was clear microscopic evidence of the RTB tract, such as haemosiderin deposition, fat necrosis, inflammation and/or fibrosis within the perinephric fat. It was in these areas that dispersed tumour cells were identified; these cells were discontinuous with the main tumour and thus deemed unlikely to represent direct perinephric fat invasion (**Figure 2**).

Figure 2

Occasionally, a further clue to the site of biopsy is the presence of absorbable gelatin (Gelfoam®), a substance used by some radiologists to reduce the risk of post-biopsy bleeding, which has characteristic histological features (**Figure 3**).

Figure 3

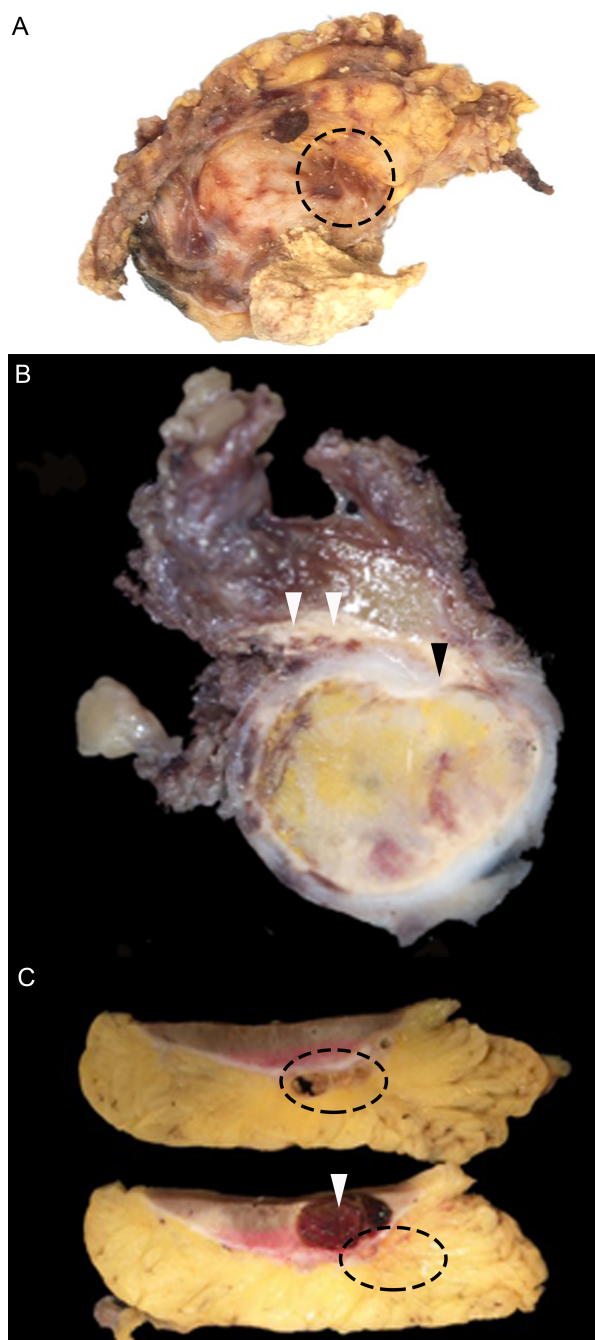
The clinical significance of tumour upstaging due to RTB tract seeding remains to be defined⁵ and we do not advocate deviation from current clinical guidelines. Indeed, RTB tract seeding has not been identified in several large retrospective case series examining outcomes following RTB⁶⁻⁹ or in a systematic review of the topic,¹⁰ although it is not clear whether biopsy tract features were identified histologically in the cases included in these studies. However, histological evidence of seeding was also not identified in two smaller studies in which the perinephric fat from post-biopsy nephrectomy specimens was routinely examined in its entirety.^{11, 12} Description of RTB seeding is therefore limited to several case reports and our own case series.⁴ Interestingly, almost all cases of seeding reported to date have been associated with PRCC, which may relate to structural features particular to this tumour type.¹³ There are now two published cases, including one in our own series, in which there has been subsequent histologically proven local tumour recurrence at a site consistent with prior RTB.^{3, 4} Furthermore, a recent review of almost 25000 clinical T1a RCC cases from the United States National Cancer Database reported an association between RTB and upstaging due to perinephric fat involvement (2.1% amongst RTB patients versus 1.1% amongst non-RTB patients, $P < 0.01$) and that upstaging was associated with poorer overall survival.¹⁴ However, the authors acknowledged the lack

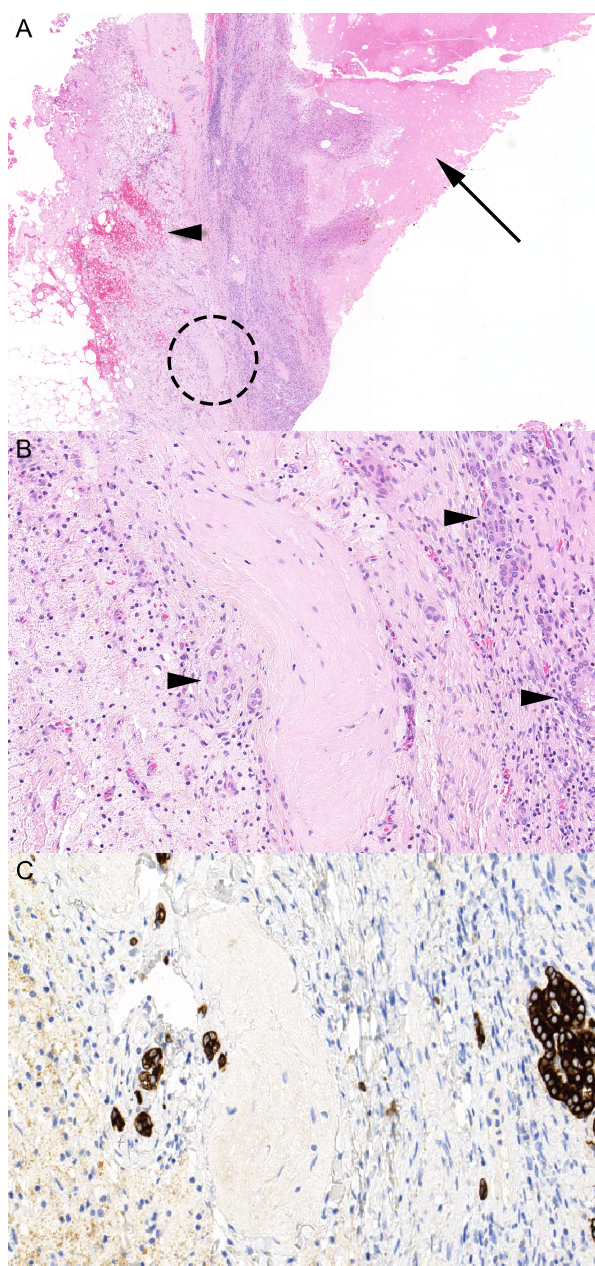
of histological evidence to distinguish upstaging due to RTB tract seeding from that due to direct perinephric fat invasion.

There have been several publications in recent years on the macroscopic examination, handling and staging of renal tumour specimens and only one of these alludes to RTB tract seeding.¹⁵ This study, assessing interobserver variability among specialist urological pathologists when staging RCC, mentions discordance in staging of a case of PRCC in which a few tubules were present in the loose tissue at the perinephric interface at a site suggestive of a biopsy tract. Only 48% of respondents had specific criteria for identifying biopsy tract features (including a documented history of prior RTB, the presence of haemorrhage or haemosiderin and a linear distribution of tumour). These findings support the need to increase awareness of this phenomenon amongst practising pathologists. Based on our experiences, we would advise pathologists to confirm whether or not there has been a previous RTB prior to dissection of tumour nephrectomy specimens. If there has been a biopsy, we recommend blocking the entire RTB tract (if identifiable macroscopically) and associated surgical resection margin. This will facilitate better appreciation of the true incidence of seeding, which currently may be under-recognised. Importantly, this will support the accrual of more mature data concerning the clinical significance, if any, of RTB tract seeding.

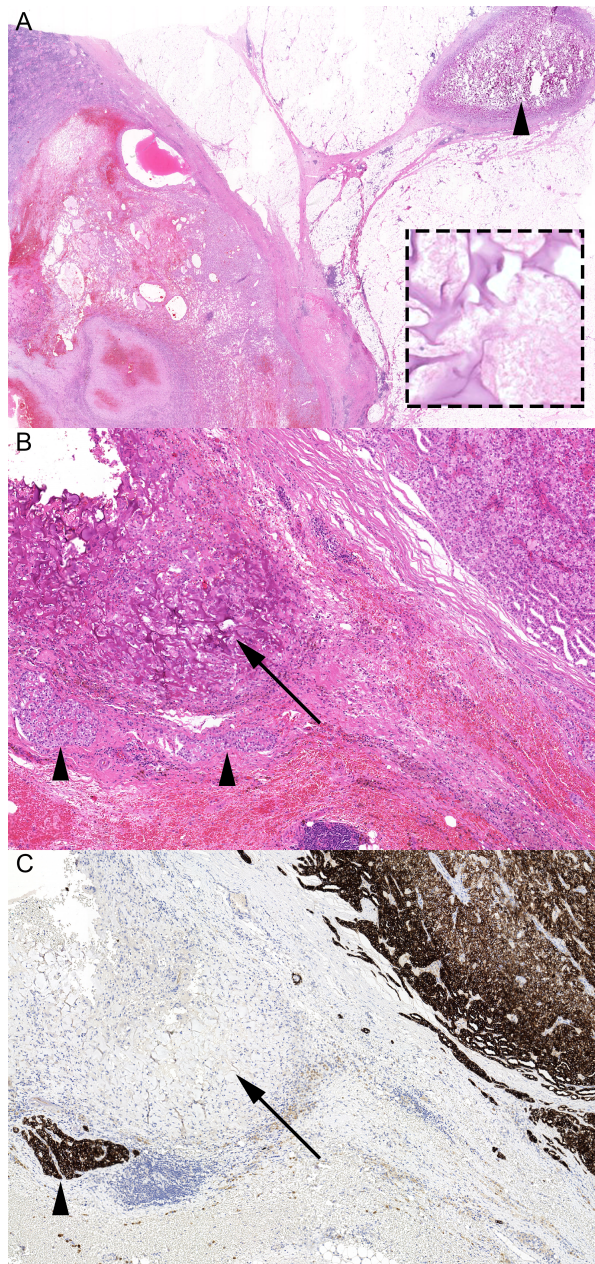
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