To the Editor:

Rini et al. reported that thrombotic microangiopathy (TMA), a potentially life-threatening toxicity resulting from vascular endothelial growth factor (VEGF) inhibition, may be more likely in uninephrectomized renal cell carcinoma (RCC) patients, while no patient with a non-RCC malignancy in their cohort experienced TMA [1]. Literature review as well as our personal data casts doubt on the importance of a solitary kidney in TMA resulting from VEGF inhibition [2–10] (Table 1). In 18 TMA reported cases in literature, only 6 cases of RCC patients who had experienced nephrectomy, chronic kidney disease, diabetes and hypertension have been mentioned [3,8–10]. In our personal experience (unpublished data), only 5 out of 20 TMA cases had metastatic RCC (mRCC), underwent nephrectomy and had hypertension. The other 12 literature cases [2,4–7] (66.6%) as well as our own 15 remaining TMA cases (75%) had both kidneys, and <26% of them were diabetic and/or hypertensive and/or renal insufficient (Table 1). TMA related to anti-VEGF–VEGFR agents (anti-VEGF agent such as bevacizumab or VEGF Trap, or VEGFR inhibitors such as sunitinib, sorafenib or pazopanib) is clearly a class effect, and the underlying renal and oncological conditions can, at best, be considered an undiscriminating predisposing factor. Moreover, the pathophysiology of TMA induced by the combination bevacizumab and sunitinib is clearly in relation to VEGF pathway inhibition.

Fifty percent of our patients did not show haematoologic signs of TMA. Despite the fact that TMA related to anti-VEGF therapy might be selectively of renal expression, only half of the biopsied patients had grade 3 or 4 proteinuria. Therefore, TMA is under-diagnosed, and clinicians should be more attentive to mild renal anomalies in those patients. Patients showing proteinuria need special referral to nephrologists. Close follow-up of hypertension and/or proteinuria in all patients by the oncologists cannot be overemphasized.

Conflict of interest statement. None declared.

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Table 1. Characteristics of patients who developed TMA related to anti-VEGF agents: RCC vs non-RCC malignancies

| Parameters | Case reports | Our cohort |
|------------|--------------|------------|
|            | mRCC | Non-RCC malignancy | mRCC | Non-RCC malignancy |
| Median (range) | n = 6 | n = 12 | n = 5 | n = 15 |
| Age, years | 62 (57–70) | 59 (44–74) | 56.5 (20–73) | 70 (57–74) |
| Previous nephrectomy | 6 | 0 | 4 | 0 |
| Hypertension | 1 | 0 | 3 | 3 |
| Diabetes | 1 | 1 | 0 | 1 |
| Renal insufficiency | 4 | 1 | Not available | 1 |
| Bevacizumab | 3 | 9 | 3 | 10 |
| VEGF Trap | 0 | 1 | 0 | 5 |
| Sunitinib | 3 | 2 | 2 | 0 |
| Proteinuria | 7 (5–10.6) | 3.4 (0.16–16.6) | 1.96 (0.37–16.6) | 1.6 (0.5–3.72) |
| Pu <2 g/day | 0% | 25% | 60% | 40% |
| SBP, mmHg | 206 (157–220) | 180 (160–210) | 160 (110–190) | 160 (155–190) |
| DBP, mmHg | 114 (100–130) | 100 (90–110) | 90 (70–120) | 105 (90–110) |
| Creatinine, mg/dL | 1.7 (1.7–4.1) | 2.6 (0.9–5.7) | 0.98 (0.46–1.96) | 0.96 (0.87–1.28) |
| Haemoglobin, g/L | – | – | 13.5 (9.1–13.5) | 10.7 (8.6–14.1) |
| Platelet, G/mL | – | – | 85 (29–184) | 176 (40–400) |
| Schizocytes (positive) | – | – | 50% | 50% |
| Haptoglobin, g/L | – | – | 1.82 (0.1–2.69) | 1.28 (0.1–3.58) |
| LDH, IU/mL | – | – | 562 (370–950) | 542 (400–2202) |

TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor; RCC, renal cell carcinoma; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDH, lactic dehydrogenase.
Subcutaneous haematoma caused by insulin injection is a very rare complication [1–3]. One report described that inappropriate maneuver of insulin injection triggered haemorrhagic shock [2]. Although our case had several risk factors, such as chronic kidney disease, diabetes, rheumatoid arthritis, post-operative state and usage of warfarin, insulin injection was used properly. The fact that haemorrhagic shock occurred in this case is a warning of possible complications of insulin injection in high-risk patients.

Although fine needles are remarkably thin, therefore considerably reducing the risk of haemorrhage [4], lethal subcutaneous haematoma could happen even in a careful clinical setting.

Discussion

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