Case report

Development of pyogenic granuloma with strong vascular endothelial growth factor-receptor-2 expression during ramucirumab treatment

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SUMMARY
The angiogenesis inhibitor ramucirumab (IMC-1121B) is a fully humanised IgG1 monoclonal antibody targeting the extracellular domain of vascular endothelial growth factor receptor 2. Ramucirumab has been approved as a second-line treatment for lung cancer. Pyogenic granuloma is an acquired, benign vascular tumour of the skin or mucous membrane. We encountered a patient with pyogenic granuloma who was treated with ramucirumab. The patient was a 48-year-old Japanese woman with advanced lung cancer who had been heavily pretreated using several lines of chemotherapy. Ramucirumab was administered as the fifth-line treatment with docetaxel. After 10 days, a painless rice-coloured or pink papule appeared on her finger. One month later, it increased in size to 20 mm (figure 1).

OUTCOME AND FOLLOW-UP
The tumour was surgically resected owing to a suspicious malignant metastasis. After PG resection, there was no recurrence. Unfortunately, docetaxel plus ramucirumab was discontinued due to progressive disease.

BACKGROUND
Pyogenic granuloma (PG) is an acquired, benign vascular tumour of the skin or mucous membrane. PG is considered a reactive tumour-like lesion, arising from various stimuli, such as chronic low-grade irritation, traumatic injury, hormones or drug-induced reactions. PG development during chemotherapy has rarely been reported, including only one known case of PG development during ramucirumab administration1 where a proliferative disease. H&E staining of the resected tissue specimen revealed an epidermis-covered protuberant lesion showing irregular proliferation. Histopathological findings were consistent with PG (figure 2A).

For immunostaining, heat-induced antigen retrieval was performed by incubating sections with 10 mM Tris base containing 1 mM ethylenediaminetetraacetic acid (pH 9.0). To detect VEGFR2, a section was incubated with an anti-VEGFR2 rabbit monoclonal antibody (clone 5B11; Cell Signaling Technology, Danvers, Massachusetts, USA), followed by incubation with an anti-rabbit peroxidase polymer (Nichirei Bioscience, Tokyo, Japan). The reaction products were developed with a diaminobenzidine solution (Dako, Glostrup, Denmark). Thymidine kinase-1 (TK1) and cluster of differentiation (CD31) double immunostaining were performed using an anti-TK1 mouse monoclonal antibody (clone F12; Bio-Rad, Hercules, California, USA) and anti-CD31 rabbit monoclonal antibody (clone EP3095; Abcam, Cambridge, UK). The results were consistent with PG.

CASE PRESENTATION
A 48-year-old woman was referred to us due to a chest abnormality detected during an annual health examination in March 2012. A chest CT scan showed a mass in the left lower lobe, along with the presence of pleural nodules. Diagnostic transbronchial lung biopsy showed pulmonary adenocarcinoma classified as stage IV (T4N3M1a). Combination chemotherapy with carboplatin and pemetrexed plus bevacizumab was started; however, an ALK fusion gene mutation was detected during the initial treatment. The disease returned after first-line treatment, and the patient was sequentially treated with crizotinib, alectinib and nivolumab. Ten days after the administration of docetaxel and ramucirumab, a painless rice-to-pink-coloured papule appeared on the right thumb distal interphalangeal joint. The tumour bled occasionally and did not shrink. One month later, it increased in size to 20 mm (figure 1).

Figure 1 Pyogenic granuloma: macroscopic findings. A pedunculated tumour of approximately 20 mm was seen on the right thumb DIP joint. DIP, distal interphalangeal joint.
Vascular tumours are commonly found in the face and in boys than in girls; however, in adults, it is more common in the limbs; however, their cause is not yet clear.

Recently, there have been reports of PG associated with gefitinib treatment. During ramucirumab treatment, it would be important to pay attention to the appearance of vascular lesions, which may occur at the sites of small wounds.

**Learning points**

- Pyogenic granuloma (PG) is an acquired, benign vascular tumour of the skin or mucous membrane.
- Positive staining for vascular endothelial growth factor receptor-2 (VEGFR2) was detected throughout the vascular tumour. The overexpression of VEGFR2 can be inferred from the anti-VEGF action of ramucirumab, promoting PG.
- During ramucirumab treatment, it would be important to pay attention to the appearance of vascular lesions.

**Findings that shed new light on the possible pathogenesis of a disease or an adverse effect**

*Figure 2* Pyogenic granuloma. Under the epidermis, capillary vessels showing leafy densification were observed. Vascular endothelial cells showed mild nuclear enlargement. Oedema, bleeding and mild inflammatory cell infiltration were seen in the interstitium. Malignant cells were not observed and findings were consistent with pyogenic granuloma (A) H&E staining; x100 (left), x400 (right)). Strong staining of VEGFR2 was observed in almost all vascular endothelial cells (B) VEGFR2 immunostaining; x400). TK1, a cell proliferation marker, was also frequently detected (C) TK1/CD31 double immunostaining; x400). VEGFR2, vascular endothelial growth factor receptor-2.

Ki-67.9–11 We found many cells positive for TK1 by immunostaining, thus indicating the proliferation of vascular cells.

Based on PG occurrence in the fingers, we hypothesised that a small wound triggered VEGFR2 overexpression by a mutation in KDR (p.T771R), which is a driver of vascular lesions, following ramucirumab administration. Positive TK1 staining suggested the vascular tumour to be growing rapidly.

There have been several reports of vascular tumour growth due to the use of angiogenesis inhibitors. However, despite the use of angiogenesis inhibitors, we found evidence for vascular tumour growth. VEGFR2 is likely to have been involved, owing to the concurrent ramucirumab administration.

In conclusion, we report a case of a vascular tumour (PG) during administration of the VEGFR2 inhibitor ramucirumab (an angiogenesis inhibitor). Therefore, during ramucirumab treatment, it is recommended to pay attention to the appearance of vascular lesions, which may occur at the sites of small wounds.

**Contributors** YH designed the study and TI wrote the initial draft of the manuscript. MT and SK contributed to pathological analysis and interpretation of data and assisted in the preparation of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Funding** This study was funded by Grant-in-Aid for Scientific Research Program from the Japan Society for the Promotion of Science (JSPS KAKENHI; Grant Number 16K08690).

**Competing interests** None declared.

**Patient consent for publication** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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7 Antonescu CR, Yoshida A, Guo T, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. Cancer Res 2009;69:7175–9.
8 Watanabe R, Nakano E, Kawazoe A, et al. Four cases of paradoxical cephalocervical pyogenic granuloma during treatment with paclitaxel and ramucirumab. J Dermatol 2019;46:e178–80.
9 Wang J, Liu Q, Zhou X, et al. Thymidine kinase 1 expression in ovarian serous adenocarcinoma is superior to Ki-67: a new prognostic biomarker. Tumour Biol 2017;39.
10 Zhou J, He E, Skog S. The proliferation marker thymidine kinase 1 in clinical use. Mol Clin Oncol 2013;1:18–28.
11 Okamura S, Osaki T, Nishimura K, et al. Thymidine kinase-1/CD31 double immunostaining for identifying activated tumor vessels. Biotech Histochem 2019;94:60–4.