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CASE REPORT

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Extramedullary plasmacytoma of the oral cavity metastasising to both kidneys in a dog

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Abstract

Background: Most extramedullary plasmacytomas (EMPs) aresolitary and located in the head and neck region. They may also occur in the visceral parts of the body.

Objectives: Here, we report a case of oral EMP followed by neoplastic plasma cell metastasis to both kidneys in a neutered male Pomeranian.

Methods: Oral plasmacytoma recurred 11 months aftersurgical removal of an oral mass and partial maxillectomy was performed. Eighteen months after partial maxillectomy, neoplastic masses were detected in both kidneys on computed tomography. The dog died 12 months after detection of bilateral kidney neoplasms. The resected neoplastic masses were routinely processed for histopathological observation and immunohistochemistry against pan-cytokeratin, desmin, CD3, and MUM-1.

Results: The recurred mass mainly consisted of well-differentiated plasma cells and contained a small portion of aggressive cells with malignant features. Monoclonal gammopathy was not observed on serumelectrophoresis performed to exclude multiple myeloma. The mass was composed of plasma cells with high nuclear pleomorphism and abundant mitotic figures. The neoplasm stained positive for MUM-1 with a more aggressive morphology than in oral EMP.

Conclusion: Based on serum biomarker and pathological observations, a diagnosis of recurrence and metastasis of oral-to-renal EMP was established. To the best of our knowledge, metastasis of oral EMP into the bilateral kidneys, as described in the current case, has not been previously reported in dogs.

KEYWORDS
dog, extramedullary plasmacytoma, kidney, metastasis, recurrence

1 | INTRODUCTION

Oral extramedullary plasmacytomas (EMPs) are uncommon tumours that rarely metastasise in dogs. These neoplasms are composed of plasma cells derived from B lymphocytes (Miller et al., 1998). EMPs represent 2.4% of all canine neoplasms, and the most common location is the skin (86%), followed by the oral cavity (9%), and gastrointestinal tract (4%) (Kupanoff et al., 2006). EMPs are usually found in middle-aged to older dogs between the ages of 9 and 10 (Clark et al., 1992; Rakich et al., 1989; Ramos-Vara et al., 2007).

Although EMPs have relatively good prognoses in humans, metastasis and progression to multiple myeloma, a more systemic and severe form of plasma cell neoplasm, can occur in 20%–40% of the patients (Holland et al., 1992; Nofsinger et al., 1997). Severe cases of EMPs can precede multiple myeloma (Shah et al., 1982). Additionally, in humans, EMPs may exist as solitary lesions or coexist with multiple myeloma (Nangia et al., 2011; Yang et al., 2013). The majority of EMPs in humans occur in the head and neck regions, with lower frequency in other sites, such as the gastrointestinal tract, central nervous system, thyroid, breasts, kidneys and lymph nodes (Alexiou et al., 1999; Reed et al., 2011; Zhang et al., 2013).

Conversely, in dogs, it is broadly accepted that EMPs do not progress to multiple myeloma (Baer et al., 1989; Johnson et al., 2021). Cutaneous and oral EMPs in dogs are generally benign, and surgical removal usually results in a good prognosis (Clark et al., 1992; Ehrensing & Craig, 2018; Rakich et al., 1989; Schrenzel et al., 1998; Wright et al., 2008). Cases of the development of multiple myeloma after the diagnosis of solitary EMP have been reported in dogs (Aoki et al., 2004; Lester & Mesfin, 1980; Morton et al., 1986; Walton & Gopinath, 1972); however, the recurrence or metastasis of oral EMP after a successful surgery is rare (Cangul et al., 2002; Pargass et al., 2017).

The present study describes the case of a dog with oral EMP that recurred after primary surgical excision. Following a partial maxillectomy performed after recurrence, renal plasma cell tumours with aggressive histology were found in both kidneys.

2 | CASE DESCRIPTION

A 10-year and 8-month-old neutered male Pomeranian was admitted to a local clinic in South Korea for examination of an oral mass in the maxillary area between the 101 and 102 incisors. The mass was a pink, smooth, elastic, solitary polyp-like lesion sized 0.5 cm × 0.5 cm (Figure 2a, left). The patient did not present with any clinical signs besides pre-existing tracheal collapse. The mass was surgically removed by local excision (Figure 2a, right). No additional histological or medical examinations were conducted.

Eleven months after the first incidence, an oral mass recurred in the same region (Figure 1). The oral mass was 0.7 cm × 0.7 cm in size, reddish in colour with soft and bulging texture (Figure 2b). It showed aggressive growth and was bleeding with a noticeably unfavourable scent. The dog expressed discomfort by frequently licking the mass and refusing physical contact. The spaces between the incisors surrounding the mass became wider and the teeth loosened over time.

Whole-body Computed tomography (CT) (Aquilion, Toshiba, Japan) revealed an ill-defined, attenuating soft-tissue mass with contrast enhancement in the maxillary area between the 101 and 102 incisors (Figure 2c and d). The oral mass was removed using partial rostral maxillectomy. The surgical margins were clear and sufficient margins were removed. The left caudal margin was approximately 1.7 mm wide, dorsal margin was 0.4 mm, right caudal margin was 3.7 mm, and middle caudal margin was 1.3 mm wide. Surgery was considered successful, and the oral neoplasia did not recur after partial maxillectomy until death.

Histopathological analysis revealed that the mass consisted of neoplastic round cells having distinct cytoplasmic margins with abundant, dense, brightly eosinophilic cytoplasm, and oval, coarsely stippled nuclei that were often eccentrically located. The round cells were linearly arranged accompanying thin fibrous stroma, seldom forming sheet or nest. Taken together, the mass was identified as oral extramedullary plasmacytoma. The overall histology showed a benign morphology with low pleomorphism (Figure 3a), but invasive characters were occasionally detected (Figure 3b). No apparent associated tumour symptoms such as weight loss, anorexia or vomiting, were observed.

Eleven months after the partial maxillectomy, the dog was examined as part of a routine check-up clinically (Figure 1). In the whole-body radiograph, there were no signs of bone lysis. CBC and serum chemistry analyses also showed no specific pathological findings.

Eighteen months after the partial maxillectomy, the dog gradually exhibited inappetence, lethargy and weight loss. CBC and serum chemistry analyses showed a normal level of ALKP, marginally elevated white blood cell (WBC) count and a 7-fold higher than normal level of cCRP-P level. Whole-body CT revealed no additional recurrence of neoplasm at the previous surgery site (Figure 2e). However, multiple, well-demarcated masses in both kidneys were observed with low attenuation and heterogeneous contrast enhancement. These findings were also observed in renal ultrasonography (Figure 4a and b). Samples were collected from the right kidney using needle biopsy, and histopathological investigation was performed. In addition, a uniform population forming a solid cellular sheet was observed. These cells were positive for multiple myeloma oncogene-1 (MUM-1, rabbit monoclonal 1:200, ab124691, Abcam) protein, confirming that they were plasma cell derivatives. After diagnosis of renal tumour, medication initiated with 0.25 mg/kg prednisolone and 0.125 mg/kg melphalan via oral administration daily for 10 weeks, and every other day for the following 5 weeks (Figure 1). On inspection of the CT scan with identification of renal lesions, no signs of bone lysis were found (Figure 4c and d). Also, abnormal lymph node enlargement of the mandibular, popliteal, prescapular, axillary and inguinal nodes were not observed. Twenty-six months after the partial maxillectomy, during a medical follow-up, intermediary CBC and serum chemistry analyses showed a normal Ca^{2+} level, an elevated ALKP level, an extremely high level of cCRP-P, and a slightly elevated WBC count. Melphalan and prednisolone administration was discontinued after

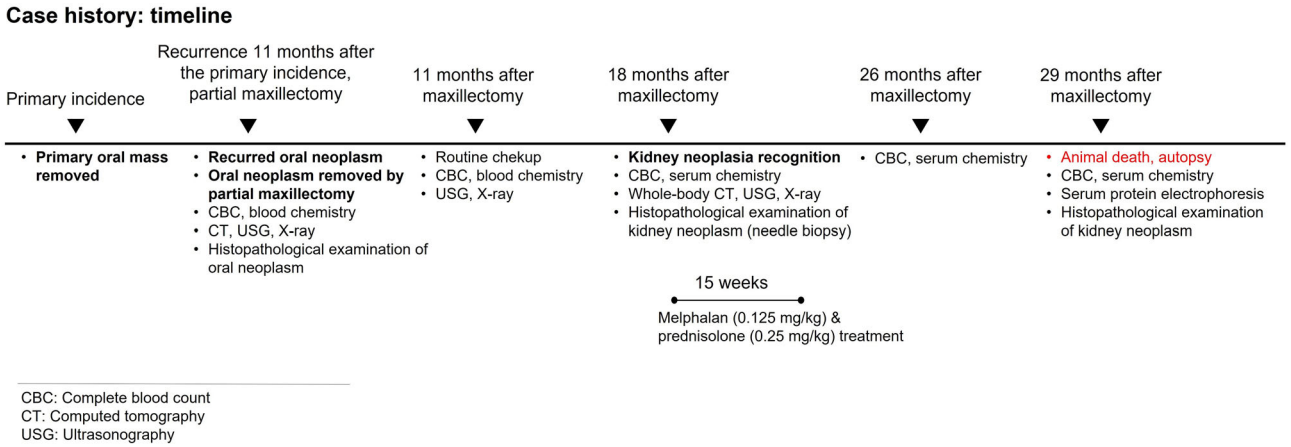


FIGURE 1 Timeline of the incidence described in the case. Oral neoplasm recurred 11 months after the primary incidence, and the patient was reassessed four times after the partial maxillectomy.

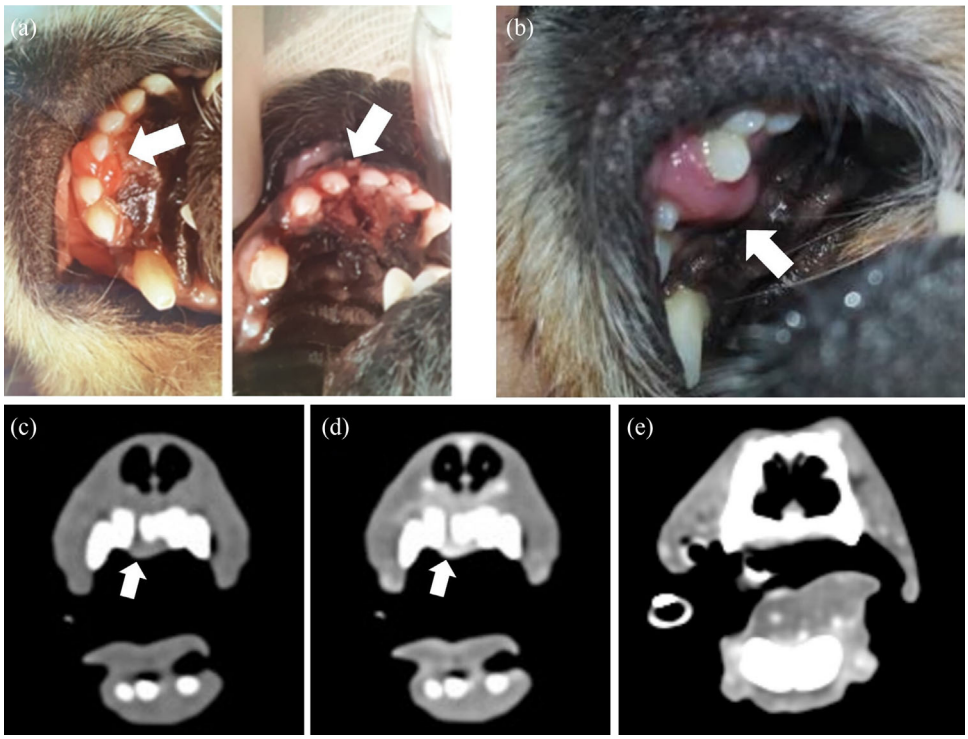


FIGURE 2 Incidence of oral plasmacytomas. (a) Left: primary incidence of oral plasmacytoma. Right: incomplete surgical removal of the neoplasia. (b) Second incidence of oral plasmacytoma 11 months after the primary incidence. The growth rate of the neoplasm was notably faster than in the primary incidence. (c–e) Computed tomography images of the oral tumour. Noncontrast (c) and post-contrast (d, e) transverse plane in a soft tissue window setting (WW 450, WL 40). Ill-defined, attenuating soft-tissue masses (arrows) with contrast enhancement in the maxillary between the 101 and 102 incisors (c, d). No sign of a mass is present in CT scan 11 months after partial maxillectomy (e).

15 weeks of treatment due to side effects such as elevated liver enzyme levels, systemic inflammation (c-CRP) and symptoms including diarrhoea.

The serum Ca^{2+} level and blood urea nitrogen (BUN)/creatinine ratio were within the normal range over 2.5 years of follow-up. However, 29 months after the maxillectomy, the dog exhibited an elevated BUN/creatinine ratio, potentially indicating renal dysfunction. Serum protein electrophoresis revealed no signs of monoclonal gammopathy (Figure 5). After the dog died, post-mortem sampling was subsequently performed. Each kidney was sampled and used for gross and microscopic examination. Irregular structures were observed in the proximal and distal areas of the right kidney and in the renal vein and renal pelvis area of the left kidney (Figure 6a). The cut surface of the sample exhibited a yellowish white colour with

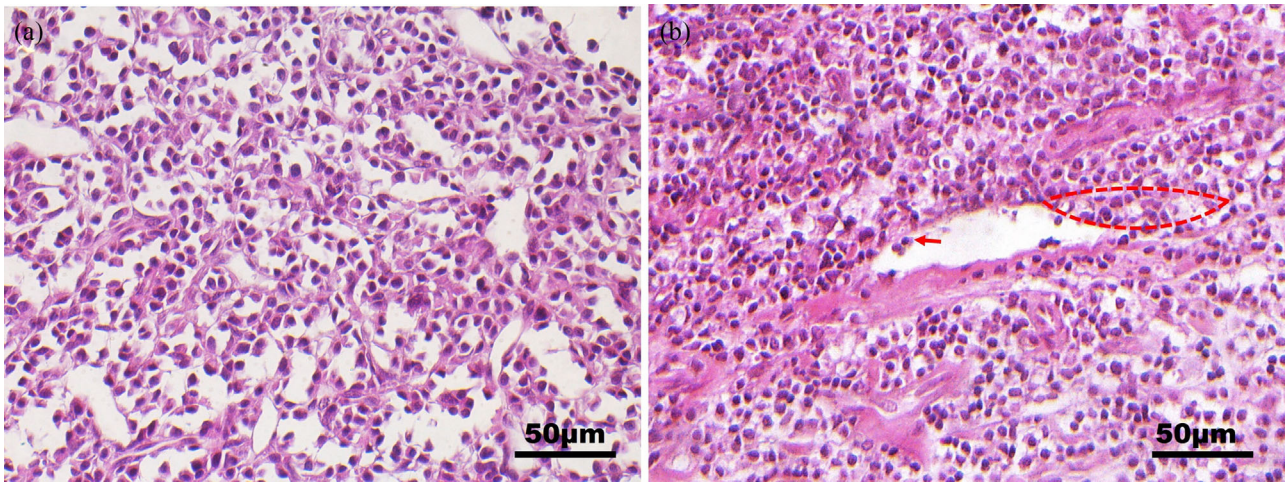


FIGURE 3 Histopathology of oral plasmacytoma. Most portion of the tumour was well-differentiated (a), but invasive characters (b) were occasionally detected, H&E, ×400.

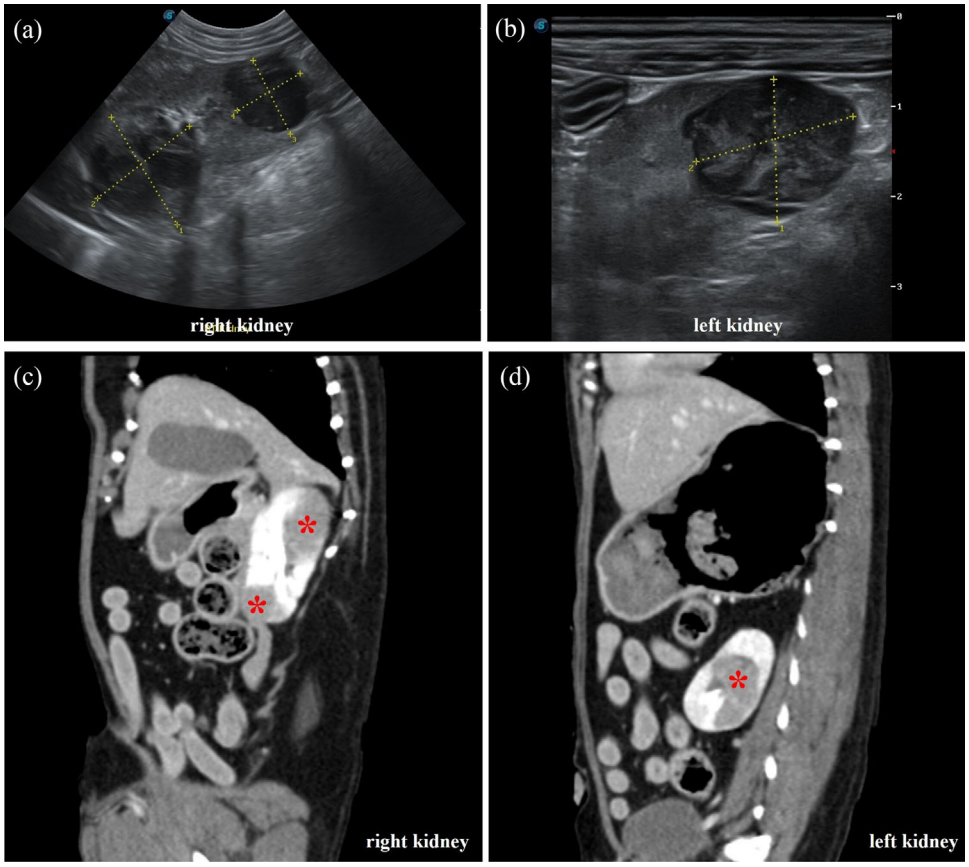
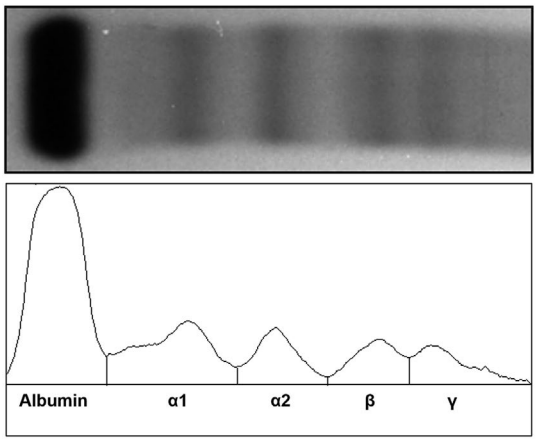


FIGURE 4 Ultrasonography and post-contrast computed tomography images in a soft tissue window setting (WW 450, WL 40) of renal tumours. The ultrasonography image (a, b) shows multiple, well-defined and heterogeneous renal nodules in the right (a) and left (b) kidneys. On post-contrast computed tomography (c, d), the renal nodules (*) have bilateral involvement and shows heterogeneous enhancement.

haemorrhagic lesions (Figure 6b). Histopathologically, the mass was mainly composed of numerous neoplastic round cells accompanied by severe fibrosis within the kidney parenchyma. The neoplastic round cells were characterised by eccentric round nuclei with abundant eosinophilic cytoplasm arranged in dense sheets or nests supported by fibrous stroma, most of which were poorly differentiated. Additionally, several multinucleated cells were found, and nuclear pleomorphism was high with abundant mitotic figures (Figure 7a and b).



Fractions	Percentage (%)	Concentration (g/dL)	Reference range (g/dL)
Albumin	52.10	2.81	2.72 - 4.49
Alpha 1	20.56	1.11	0.34 – 0.91
Alpha 2	10.72	0.58	0.24 – 0.96
Beta	8.92	0.48	0.51 – 1.65
Gamma	7.70	0.42	0.23 – 1.07

Total protein: 5.4 g/dL

FIGURE 5 Serum protein electrophoresis results from sample collected 29 months after partial maxillectomy. Monoclonal gammopathy was not observed.

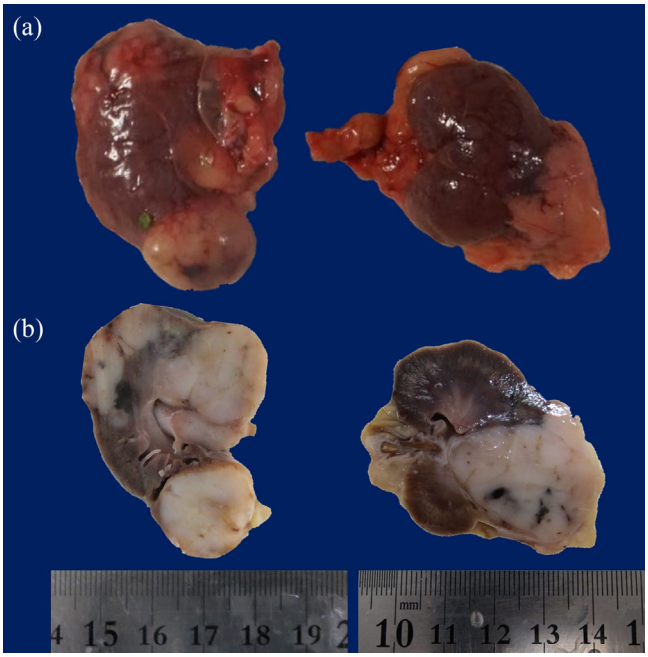


FIGURE 6 (a) Post-mortem images of the right kidney (left) and left kidney (right). Irregular structures are observed in the proximal and distal areas of the right kidney, and in the renal vein and renal pelvis area of the left kidney. (b) The cut surface of the formalin-fixed kidney is shown.

Immunohistochemistry was performed for pan-cytokeratin (mouse monoclonal 1:200, ab86734, Abcam, Cambridge, UK), desmin (mouse monoclonal 1:200, sc-23879, Santa Cruz Biotechnology, Dallas, TX, USA), CD3 (rabbit polyclonal 1:200, A0452, Dako, Glostrup, Hovedstaden, Denmark) and MUM-1 (rabbit monoclonal 1:200, ab124691, Abcam); additionally, toluidine blue staining was performed for differential diagnosis (Figure 7c–h). Negative staining for pan-cytokeratin ruled out tumours of epithelial cell origin, such as renal cell carcinoma (Figure 7d). Moreover, negative staining for CD3 and desmin ruled out lymphoma of T-cell origin (Figure 7f) and rhabdomyosarcoma (Figure 7e). Negative toluidine blue staining ruled out a mast cell tumour (Figure 7c). However, the cells stained positive for MUM-1, confirming that they were plasma cells derived from B-type lymphocytes (Figure 7g and h). Taken together, these findings confirmed neoplasms in both kidneys that were diagnosed as metastatic renal extramedullary plasma cell tumours.

3 | DISCUSSION

The dog in this case showed recurrence of oral plasmacytoma in the same region 11 months after the initial incidence, with signs of aggravation such as brittleness and bleeding. CT revealed local bone lysis in the rostral maxilla, which has been reported in the previous cases of oral EMP (Pargass et al., 2017; Smithson et al., 2012). Oral plasmacytomas are usually benign and have good prognoses after local surgery. The recurrence rate of oral EMP after surgical excision has been reported to be low (Cangul et al., 2002; Pargass et al., 2017; Rakich et al., 1989; Schrenzel et al., 1998), with recurrences attributed to the remaining neoplastic cells at the surgical margins (Clark et al., 1992; Wright et al., 2008). These previous studies suggest that the tumour recurrence in the current case was due to incomplete surgical resection. However, after partial maxillectomy, the oral plasmacytoma no longer showed any signs of recurrence.

The relationship between oral and kidney plasmacytomas is unclear. As neoplasms were observed in two different areas of the patient, the possibility of multiple myeloma was considered. It is conceivable that oral and kidney EMPs developed secondary to multiple myeloma. However, the patient showed no evidence of osteolytic lesions in the vertebra, femur, or humerus on whole body CT or X-ray examination, which are commonly observed in multiple myeloma patients in both dogs and humans (Auger et al., 2021; Bataille et al., 1992). In addition, over 2.5 years of long-term observation and laboratory examination, CBC and blood chemistry analyses revealed no evidence of anaemia, thrombocytopenia, leukopenia, and noticeable hypercalcaemia, which are symptoms associated with systemic multiple myeloma (The

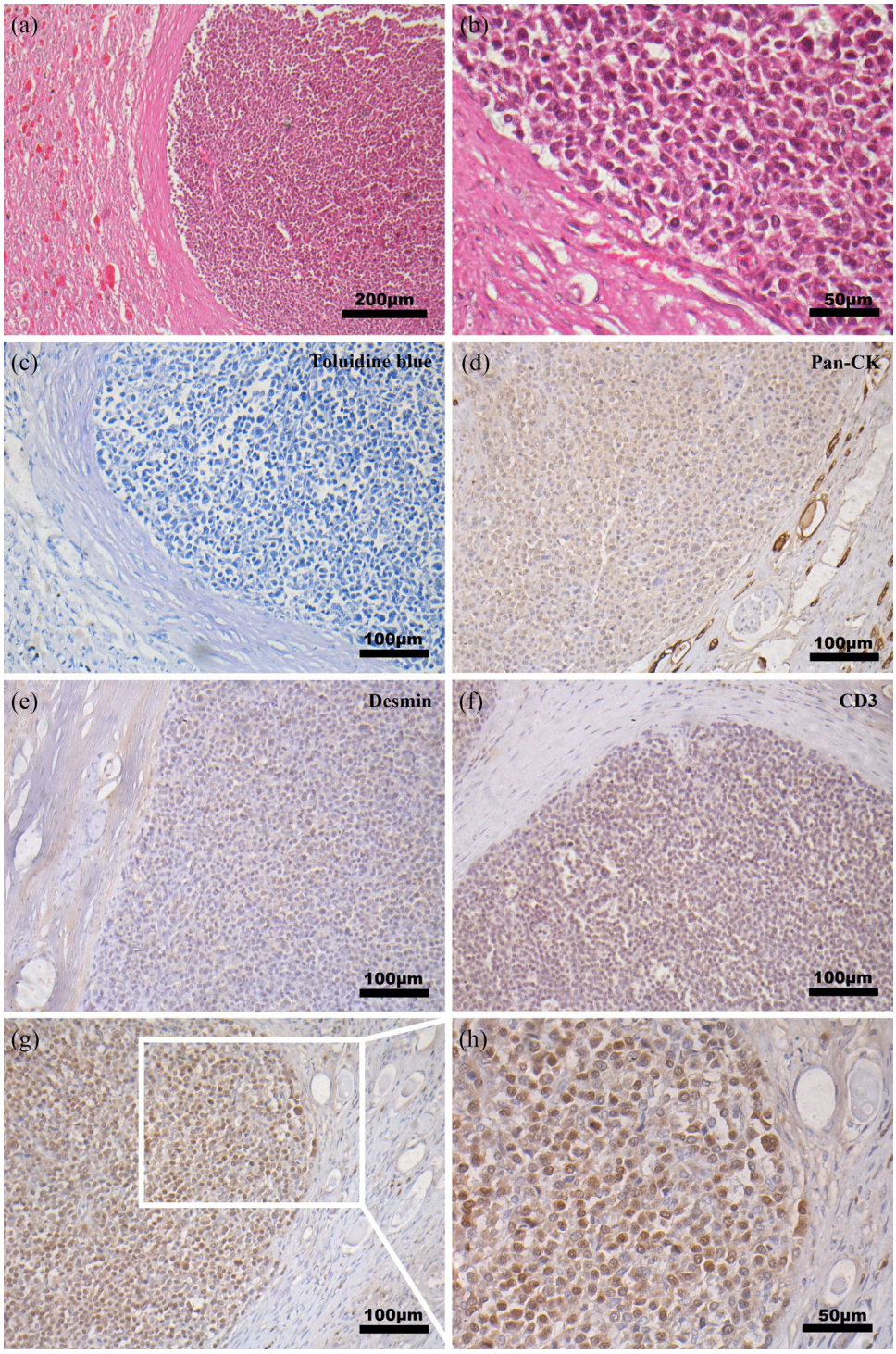


FIGURE 7 Histopathological examination of kidney neoplasm. (a, b) Haematoxylin and eosin staining. (c) The neoplasm was negative to toluidine blue staining. Immunohistochemistry was performed, and the neoplasm was negative to pan-cytokeratin (d), desmin (e) and CD3 antibody (f). The kidney tumour was positive to MUM-1 antibody (g, h).

International Myeloma Working Group, 2003; Fernández & Chon, 2018; MacEwen & Hurvitz, 1977).

Assessment of monoclonal proteins (M-proteins) in the serum is important for distinguishing B-cell neoplasia disorders (The International Myeloma Working Group, 2003). The dog in this case showed normal or only marginally elevated total globulin levels in blood chemistry analysis, and serum electrophoresis showed no evidence of monoclonal gammopathy (Figure 5). Gammopathy is typically associated with multiple myeloma. In humans, M-protein is present in the serum or urine of approximately 97% of patients with multiple myeloma; however, EMP generally does not accompany gammopathy (Harris et al., 2019; Pargass et al., 2017; Soutar et al., 2004; The

International Myeloma Working Group, 2003). In 3% of cases, M-protein is not detected in patients with multiple myeloma, and these cases are known as nonsecretory myeloma (The International Myeloma Working Group, 2003). Cases of nonsecretory myeloma have rarely been reported in dogs and were accompanied by other features of multiple myeloma, such as multifocal masses, plasma cell infiltration in bone marrow aspirates, and/or systemic bone lysis (Elliott, 2014; Marks et al., 1995; Sakai et al., 2008; Souchon et al., 2013). In this case, the masses were confined to the kidneys, and systemic bone lysis was not detected. Therefore, based on the available evidence, it seems unlikely that oral and kidney masses were secondary manifestations of pre-existing multiple myeloma.

We considered the possibility that the kidney neoplasm developed independently from oral EMP, because primary EMP in the kidney has been previously reported once in a dog (Johnson et al., 2021). However, histopathological analyses of the kidney plasma cell tumours showed aggressive features within the tissue, including low differentiation, high mitotic figure, eccentric nuclei and multinucleated cells (Figure 7b). In addition, histopathological investigation of the recurrent oral mass revealed signs of partially aggressive plasma cells invading the blood vessel. This indicates that the kidney neoplasms developed as a result of metastasis from a different primary tumour, most likely oral EMP, and that the patient represents a case of oral EMP developing into a systemic disease. The recurrence rate after successful excision of oral EMPs has been reported to be very low (Cangul et al., 2002; Pargass et al., 2017; Rakich et al., 1989; Schrenzel et al., 1998; Wright et al., 2008). In humans, approximately one-third of the EMPs metastasise and develop into multiple myeloma (Holland et al., 1992; Nofsinger et al., 1997). Local regression, without multiple myeloma, does not necessarily lead to a worsened prognosis (Waldron & Mitchell, 1988). The development of oral or cutaneous EMP into multiple myeloma is unusual in dogs, and studies have failed to detect a relationship between the two (Baer et al., 1989; Clark et al., 1992; Rakich et al., 1989; Wright et al., 2008). One case in which a solitary plasmacytoma in the perianal region metastasised to organs such as the liver and spleen was reported (Lester & Mesfin, 1980). In the present case, as previously described, the oral neoplasm recurred because of insufficient surgical removal. Although partial maxillectomy had been performed, the neoplastic cells metastasised to the kidneys 7 months after complete excision of the mass, even with periodic clinical follow-up. As the initial surgical intervention did not sufficiently remove neoplastic cells, they may have spread systemically into the kidney through the lymphatic or circulatory systems. Previous studies have reported that EMPs have a good prognosis after maxillectomy; however, the current case indicates that clinicians should not ignore the possibility of fatal systemic metastasis of EMPs.

4 | CONCLUSION

Our study provides a detailed clinical report of an unusual case of recurring oral EMP and potential metastasis to the kidneys in a dog. We draw two main conclusions from this case study. First, proper surgical removal of the oral EMP is crucial for preventing recurrence or metastasis. Second, systemic metastasis of EMP should be considered, even after complete surgical removal.

AUTHOR CONTRIBUTIONS

Kyung Ho Park: conceptualisation; data curation; methodology; project administration; resources; writing – original draft. Tae-Un Kim: data curation; formal analysis; investigation; methodology; visualization; writing – original draft. Seoung-Woo Lee: formal analysis; investigation; methodology. Su-Min Baek: formal analysis; investigation; methodology. Daji Noh: investigation; methodology; writing – review & editing. Jae-Hyuk Yim: investigation; methodology. Young-Jin Lee: investigation. Dong-Ju Son: investigation. Sang-Joon Park: investigation; methodology. Seong-Kyoon Choi: methodology; resources. Kija Lee: writing – review & editing. Larry Chong Park: funding acquisition; writing – review & editing. Jin-kyu Park: conceptualisation; supervision; writing – review & editing.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest in this manuscript, and the manuscript is approved by all authors for publication.

FUNDING INFORMATION

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the animal hospital and clinic board. Additionally, the animal's owner consented to the clinical treatment and the use of related information in the publication.

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PEER REVIEW

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