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CASE REPORT

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Biological implant-associated granulomatous inflammation resulting in secondary hypercalcemia and azotemia in a dog

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Key Clinical Message

Implant associated granulomatous inflammation causing hypercalcemia can occur following use of commercial xenogeneic pericardial tissue patches in dogs. Removal of the implant can result in resolution of the hypercalcemia, suggesting a causal relationship between the tissue reaction to a xenogeneic implant and development of hypercalcemia.

KEYWORDS

biologic implant, biologic mesh, chest wall resection, fistulous tract, glutaraldehyde, granulomatous inflammation, hypercalcemia, pericardial tissue patch, spindle cell sarcoma, synthetic mesh, xenogenic

1 | CASE DESCRIPTION

A 7-year-old, 31 kg castrated male Labrador Retriever was initially presented to his primary veterinarian for a firm swelling of 1 month's duration on the left caudal thorax. Fine needle aspiration cytology was consistent with a mesenchymal neoplasm, and referral of the patient for staging and treatment was initiated. On referral examination, the patient was bright, alert, and very energetic. His vitals were within normal limits. Associated with the caudal aspect of the left rib cage, at the level of the costochondral junction, was a firm, immobile subcutaneous mass measuring 12 x 8 cm. All other physical exam parameters were within normal limits. A thoracic CT scan further characterized the mass as a well circumscribed, 7.5 cm × 3.9 cm × 7.3 cm, contrast enhancing mass causing cranial displacement of the 10-13th ribs without evidence of overt periosteal or osseous involvement (Figures 1 and 2).

Surgery was performed to excise the mass with 3 cm body wall margins, which included the distal osseous and entire chondral portions of ribs 10-13, the xiphoid process, and an approximately 2-cm portion of the axial margin of the diaphragm underlying the mass. A diaphragm advancement was performed and a commercially available glutaraldehyde processed porcine derived xenograft[a] was used to support the abdominal wall defect. The patient recovered uneventfully from surgery and was sent home the following day on standard doses of carprofen, tramadol and a 2-week course of cefpodoxime. It was recommended that the previously prescribed oclacitinib for atopy be discontinued during the 2-week post-operative period. Histopathology of the mass was consistent with a completely excised (>1.5 cm margins) grade II spindle cell sarcoma (Figure 3).

At 3 weeks following the surgery, the skin incision appeared to be healing well with no evidence of seroma formation or compromise to the repaired body wall defect. The patient was presented again 6 weeks postoperatively with the complaint of acute onset fluid accumulation under the skin in the region of the previous surgical site immediately following an episode of vigorous activity. Physical examination at that time revealed no overt evidence of body wall herniation, infection, or discomfort. Based on this, a seroma was suspected and continued activity restriction was recommended. Fluid aspiration was not performed. At 7 weeks post-operatively, the patient was presented on emergency for lethargy, hyporexia, polydipsia/polyuria (PU/PD), and intermittent vomiting. Evaluation at that time revealed progression of the

[a]PERISeal Tissue Patch, Avalon Medical. 1060 Curve Crest Blvd Suite 102, Stillwater, MN 55082. http://www.avalonmed.com/PeriSeal_Tissue_Patch.html

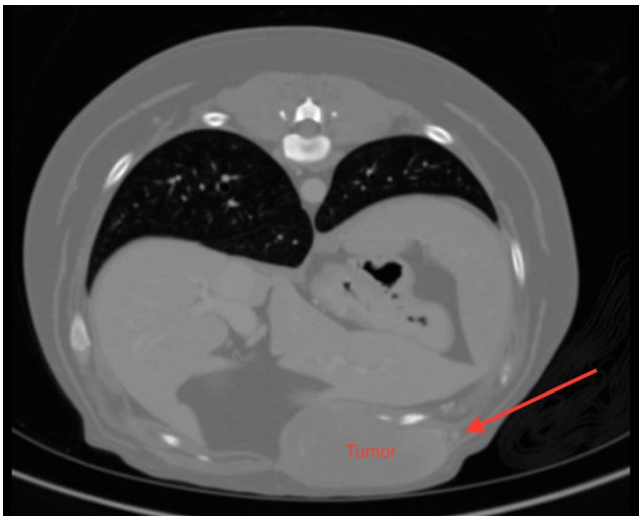

FIGURE 1 Representative axial CT image of the mass prior to surgical removal. The red arrow indicates the location of the mass

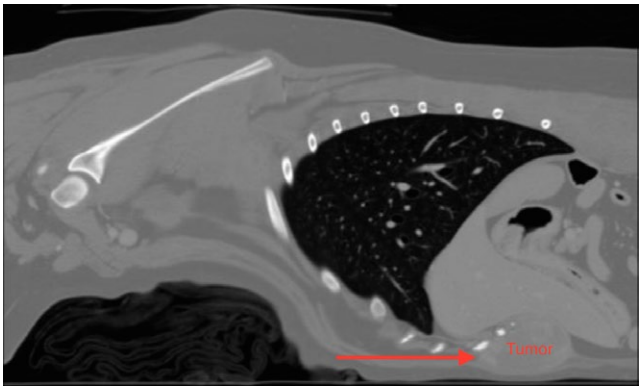

FIGURE 2 Representative sagittal CT image of the mass prior to surgical removal. The red arrow indicates the location of the mass

fluid accumulation and development of a draining tract with serosanguinous discharge and erythema associated with the left body wall surgical site. Physical exam was otherwise unremarkable, including the patient's peripheral lymph nodes and rectal examination. Blood work abnormalities included hypercalcemia (ionized calcium [iCa^{++}] of 1.76 [ref: 1.15-1.42 mmol/L] and total calcium of 16.9 mg/dL [ref: 8.9-11.3 mg/dL]) and azotemia (BUN 27 mg/dL [ref: 7.0-26 mg/dL] and creatinine 2.5 mg/dL [ref: 0.8-1.6 mg/dL]). Blood submitted to the Michigan State University Diagnostic Laboratory for measurement of paired iCa^{++}/PTH/PTHrp revealed a parathyroid hormone (PTH) concentration of 0 pmol/L (ref: 0.5-5.8 pmol/L), a parathyroid-related peptide (PTH-rp) concentration of 0 pmol/L (0.0-1.0 pmol/L), and an ionized calcium of 1.89 mmol/L (ref: 1.25-1.45 mmol/L). A sample of the fluid collected under aseptic conditions for cytology and culture revealed marked neutrophilic inflammation with scant growth of *Staphylococcus pseudintermedius* and light growth of *Pseudomonas aeruginosa*. Both

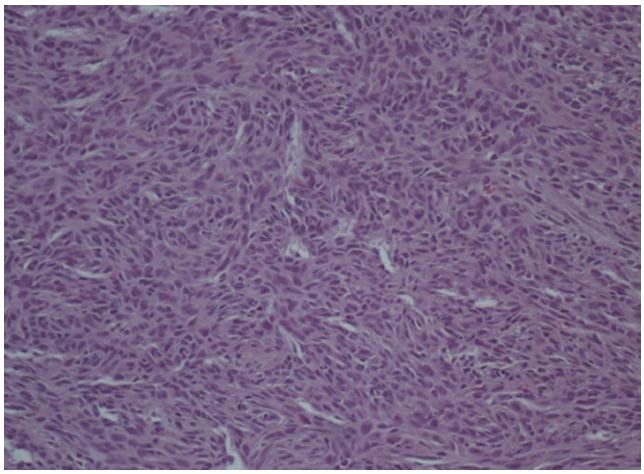

FIGURE 3 H&E stained representative section of the excised tumor displaying histological features consistent with a grade II soft tissue sarcoma

organisms showed broad antibiotic susceptibility. Ultrasound of the previous surgical site revealed a 2.4-cm fluid pocket with thick-walled undulated margins. A soft tissue mass effect was not appreciated. Ultrasound of the entire abdomen and cervical region was also performed revealing no significant abnormalities.

The patient was hospitalized for monitoring and supportive care, which included fluid diuresis with IV 0.9% NaCl + 15 mEq/L KCL, ampicillin/sulbactam (22 mg/kg IV q8h), and maropitant (1 mg/kg IV q24). Following 4 days of hospitalization, clinical signs of vomiting, lethargy, inappetence and polydipsia had resolved. He was discharged with enrofloxacin (6.5 mg/kg PO q24h) and cefpodoxime (6.5 mg/kg PO q24h) with instructions to return for a recheck in 2 days. At the time of discharge, his BUN was 14 mg/dL (ref: 7-26 mg/dL), creatinine was 1.7 mg/dL (ref: 0.8-1.6 mg/dL). His calcium remained elevated at 12 mg/dL (ref: 8.9-11.3 mg/dL).

Supportive care at home was continued until 12 weeks post operatively at which time recheck blood work showed persistent azotemia (BUN of 10 mg/dL and creatinine of 1.8 mg/dL) and hypercalcemia (total calcium of 12.1 mg/dL [ref: 8.9-11.3 mg/dL]). The surgical site discharge had subsided but the incision site remained moderately erythematous despite the 4-week course of broad-spectrum antibiotic therapy. Based on persistent tissue reaction and failure of resolution with medical management alone, surgical debridement and removal of the previously placed implant was recommended and performed. At surgery the central aspect of the previous surgical scar and the fistulous tract were excised and dissection was continued through the subcutaneous tissues until the underlying pocket was accessed. The external surface of the xenogeneic patch from the previous surgery had a yellow fibrillar coating but the patch itself was intact. The interior surface of the patch was found to be adherent

to the surface of the right medial liver lobe. A partial liver lobectomy was performed allowing for en bloc excision of all grossly affected tissue. There was no gross evidence of tumor recurrence. The abdominal wall was closed under mild tension without the need of exogenous grafting.

Histopathological evaluation of the excised implant and surrounding tissue revealed dense granulating fibrosis, edema, haemorrhage, and mixed cell (primarily mononuclear with minimal suppurative) inflammation with no visible infectious agents.

At 2 weeks post-explantation, the patient was reported to be clinically normal by his owners and he was energetic and alert on physical exam. The incision appeared to be healing well with no evidence of residual inflammation or drainage. Recheck chemistry was performed revealing resolution of the previously noted azotemia (Creatinine 1.6 mg/dL [ref: 0.8-1.6 mg/dL]) and hypercalcemia (10.4 mg/dL [ref: 8.9-11.3 mg/dL]). Repeat chemistry 8 weeks later showed persistent normalization of the patient's calcium and renal values and a staging CT scan of the thorax and abdomen was performed 9 months after explantation revealing no evidence of metastasis, tumor recurrence, or active inflammation.

2 | DISCUSSION

The clinical case reported here describes marked granulomatous inflammation and draining-tract formation with associated clinical hypercalcemia and azotemia connected with surgical placement of a glutaraldehyde processed, xenogeneic pericardial patch used for a body wall reconstruction.

When addressing large body wall defects, several options for primary repair can be considered, including direct apposition of the wound edges when possible, harvest and placement of an autogenous fascial or muscle flap, or use of exogenous materials such as surgical meshes, synthetic patches, and various biological materials.[1,2]

Direct apposition of the wound edges is often not possible due to the size of the defect and the tension that results upon closure. Therefore, in many instances, reconstruction with either autogenous or exogenous structural materials is necessary. The benefit of utilizing the patient's muscle or facial tissue for closure is that all tissues are biocompatible and complete integration of the tissue occurs through the process of natural healing. In this patient, we did not harvest local tissues due to concern for incomplete surgical margins at the time of the original surgery, and to avoid unnecessarily increasing the size of the surgical field. The primary disadvantage of harvesting autologous tissue for primary closure is that surgical field is often increased. This results in greater morbidity and potential surgical field contamination if tumor margins are incomplete. This also leads to creation of a larger treatment field should adjuvant radiation therapy be indicated. These disadvantages can be appeased through the use of exogenous materials. A variety of such materials is available to the surgeon and can be broadly categorized as either synthetic or biologic meshes. Synthetic meshes may be either permanent or absorbable.

Permanent meshes are composed of polypropylene, polyester, or expanded polytetrafluoroethylene (ePTFE) and incorporate well into surrounding tissue. However, these materials often elicit an inflammatory response that can contribute to adhesion formation with subsequent pain and loss of tissue elasticity. This is of particular concern when the mesh is placed in apposition with serosal or pleural surfaces.[3] Other complications of permanent meshes include mesh related infections, cavitary effusion due to implant irritation, and accumulation of fluid in the subcutaneous space.[1] Composite synthetic meshes have recently become available that mitigate some of these complications. Such composite meshes include a microporous side that is designed to face the visceral aspect of the defect to prevent adhesions, and a macroporous side that enhances adhesion formation and tissue ingrowth along the parietal surface.[4]

Absorbable meshes were developed to mitigate the downsides of permanent meshes and for use in potentially contaminated fields. Due to most of their absorption times being within 90-180 days, the mesh does not persist long enough for adequate tissue ingrowth. Newer generation absorbable meshes have been designed to maintain their structure long enough to allow for tissue ingrowth, thereby balancing the pros and cons of both non-absorbable and absorbable implants.[5]

Biologic meshes can also be classified as permanent or absorbable. Such biologic meshes are commonly derived from either bovine or porcine tissues that have been de-cellularized and chemically cross-linked to leave an extracellular matrix devoid of antigenic epitopes, DNA, and other potential inflammatory mediators.[6-8] The method of such de-cellularization and crosslinking carries a heavy impact on the long-term host response to the implanted mesh. All types of biological mesh initially cause a mononuclear cell infiltrate; however, the long-term remodelling response varies. Remnant DNA has been implicated as a cause of persistent inflammatory reactions following mesh implantation;[9] however, a threshold amount of DNA is required to adversely affect the remodelling response. The existing mesh processing methods, if adhered to, appear to remove enough DNA to prevent adverse events.[7] Cross-linking, a process whereby the collagen present within the material is chemically treated to resist degradation by collagenases improves graft strength but can also limit tissue regeneration and have effects on host responses to the implanted product.[10-13] With higher degrees of cross-linking, there is also an increased risk of host vs graft reactions and subsequent development of granulomatous inflammation and chronic fistulous tract formation.[10,11,14]

Compared to synthetic meshes, biologic meshes have the general advantage of causing less irritation and adhesion formation and consequently can be placed in direct contact with abdominal or thoracic organs.[4,5,15,16] They can also be used with less risk in contaminated tissues.[4] Reported complications associated with biologic meshes include loss of function through early degradation, stretching, infection, adhesions, fistula formation and rejection with secondary granulomatous inflammation.

In the case reported here, we elected to utilize an implantable biologic mesh, specifically a commercially available porcine pericardial graft[a] due to its strength, handling properties, and reported biocompatibility. The product is reported as a "durable, non-absorbable, stabilized pericardium patch" with "proprietary processing (that) yields an acellular, cross-linked tissue with exceptional handling, elasticity, and biocompatibility".[17]

Reported possible adverse reactions include those noted for any tissue implanted material such as infection, seroma formation, inflammation, adhesions, hematoma, and fistula formation.[14,15] The product[a] is supplied sterile in a 0.75% phosphate-buffered glutaraldehyde solution. Glutaraldehyde is a common fixative used for processing xenogeneic tissues for implantation into human and canine patients alike. Manufacturer recommendations include thoroughly rinsing of the patch prior to implantation, which includes submersion in sterile saline with 5 minutes of gentle swirling within the solution. While these recommendations were strictly followed during the pre-implantation process in this case, it is possible that residual glutaraldehyde on the patch lead to the inflammatory reaction observed. Residual glutaraldehyde on implanted material has been shown to induce an inflammatory reactions and hypersensitivities to fixatives in general and glutaraldehyde specifically have been reported.[13,18,19] Therefore, it is possible the patient in this report simply mounted a response to the glutaraldehyde rather than the xenogeneic patch itself, especially knowing this patient's history of severe atopy.

The association between granulomatous inflammation and calcium dysregulation has been well established in humans; however, there are few reports of hypercalcemia secondary to granulomatous disease in dogs.[20-22] Granulomatous inflammation is suspected to be the underlying cause of the hypercalcemia in this case based on the observation that the hypercalcemia developed after removal of the tumor and placement of the implant, and resolved once the implant and associated granulation tissue were removed. Definitive proof of a cause and effect relationship is not possible, however, due to the retrospective nature of this clinical case report.

The mechanism of granulomatous inflammation induced hypercalcemia is incompletely understood. One proposed mechanism includes the production of 1,25 dihydroxyvitamin D by immune cells including macrophages involved in the granulomatous reaction.[22] Other reports show granulomatous disease induced hypercalcemia occurring in the absence of an elevated 1,25 dihydroxyvitamin D, 25-hydroxyvitamin D, or other calcium regulators.[23] In the case presented here, we are unable to conjecture at the underlying molecular mechanism since vitamin D and its metabolites were not measured.

In addition to granulomatous inflammation, hypercalcemia in the dog can occur secondary to many etiologies including primary hyperparathyroidism, humoral hypercalcemia of malignancy, renal failure, hypoadrenocorticism, and vitamin D toxicosis.[24] Hypercalcemia of malignancy is the most common cause of hypercalcemia in the dog, with T cell lymphoma and apocrine gland adenocarcinoma of the anal sac being common neoplastic causes.[24,25] Other malignancies causing hypercalcemia include more rare PTH-rp secreting tumors and in even more rare cases of osteolytic tumors (ie multiple myeloma).[24] To our knowledge, no descriptions of hypercalcemia secondary to a soft tissue sarcoma in dogs have been reported.

Primary hyperparathyroidism was ruled out based on the PTH concentration being 0 mmol/L and a normal cervical ultrasound exam. Similarly, the potential for humoral hypercalcemia of malignancy was considered less likely based on the PTH-rp being 0 mmol/L and there being no evidence of lymphoma, anal sac adenocarcinoma, or other malignancies on physical exam, abdominal ultrasound or repeat thoracic radiographs. The potential for hypercalcemia of malignancy could not be completely ruled out as there are humoral factors other than PTH-rp that can have similar parathyroid hormone-like effects.[26,27]

Because the patient had concurrent azotemia with hypercalcemia, theoretically, renal disease could have resulted in the hypercalcemia. This is considered unlikely for two reasons. First, renal failure typically results in mild elevations in PTH, phosphorus, and total calcium while ionized calcium typically remains normal. In this patient, the PTH was 0 mmol/L, phosphorus was consistently normal, and the ionized calcium was significantly elevated at a measured peak value of 1.76 mol/L. Secondly, the azotemia resolved following removal of the implant and associated granulomatous tissue. If primary renal disease were the cause for the hypercalcemia, it would not be expected that either the hypercalcemia or azotemia would resolve following removal of the implant and associated inflammatory tissue. Similarly, vitamin D toxicosis was also unlikely in this case based on the patient's normal serum phosphorus concentrations not to mention a lack of exposure to potential sources of vitamin D (toxins, plants, drugs).

It remains unknown whether the implant alone resulted in the development of the tissue reaction and secondary hypercalcemia or if it was the combination of infection along with the implant that resulted in the granulomatous inflammation and biochemical changes observed. To our knowledge,

there are no reports of *Pseudomonas* or *Staphylococcus* infections alone causing granulomatous inflammation and secondary hypercalcemia. Specific agents reported to induce granulomatous inflammation and hypercalcemia in dogs include *Aspergillus*, *Mycobacteria*, *Pythium*, *Leishmaniasis*, *Blastomyces*, and *Heterobilharzia (schistosomiasis)*[28-34] While it is possible that one of these agents may have caused the granulomatous reaction and secondary hypercalcemia in this dog, it is unlikely. This is based on the fact that no etiological agents were observed histologically, and that the patient had no travel history beyond Washington State, where, aside from *Aspergillus* and less commonly mycobacterial infections, have not been reported.

Regardless of the exact underlying contributing factors, this case demonstrates the potential for complications that can occur when using a commercially available xenogeneic tissue patch. Knowing the potential for such complications can aid in minimizing their occurrence as well as recognizing and treating such complications early in the disease process.

CONFLICT OF INTEREST

None declared.

AUTHORSHIP

All authors were involved in drafting, revising and providing intellectual content of this manuscript. KL and JP: provided primary surgical and oncological care for the patient during hospitalization. TK: provided nursing support.

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