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Case report

Inflammatory reaction to BioGlue™ masquerading as recurrence in patients with endometrial cancer: A report of two cases

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1. Introduction

BioGlue™ is a vessel sealant comprised of 45% purified bovine serum albumin (BSA) and 10% glutaraldehyde, which works by creating a mechanical seal independent of the coagulation cascade (Bhamidipati et al., 2012). It has many surgical applications, best described in the thoracic surgery literature, where it has been shown to decrease operative time and surgical blood loss (Bhamidipati et al., 2012). Rare complications have been reported including primary hypersensitivity, tissue necrosis, embolization, as well as case reports documenting a granulomatous foreign body reaction (Luthra et al., 2008).

BioGlue™ has not been well studied in the setting of oncologic surgery. Gynecologic oncology cases often involve dissection of the lymphatic tissue adjacent to the aorta and Inferior vena cava (IVC). Vessel sealants may be used in conjunction with primary repair to achieve hemostasis in rare instances of vessel injury at the time of gynecologic oncology surgery (Mısırlıoğlu et al., 2018; Spotnitz, 2014). The two cases presented herein demonstrate the clinical uncertainty that arises in the setting of radiographic findings concerning for tumor recurrence at the site of IVC repair, with a differential diagnosis that includes both benign inflammatory response to BioGlue™ and tumor recurrence.

2. Case 1

A 54 year-old underwent a robotic-assisted staging procedure for biopsy proven endometrial cancer. The case was complicated by injury to the IVC during the para-aortic lymph node dissection. Hemostasis was achieved with pressure and use of a Ray-Tec gauze, followed by 5–0 prolene suture in an interrupted figure of eight fashion. BioGlue™ surgical adhesive was applied over the primary repair to ensure hemostasis. The final pathology was consistent with Stage IB, FIGO Grade 1 endometrioid endometrial adenocarcinoma with lymphovascular invasion, and the patient received adjuvant radiation therapy.

A surveillance computed tomography (CT) scan was obtained fourteen months after the initial surgery to assess disease status one year after completion of treatment, This CT revealed an enlarged 2.9 × 1.7 × 2.9 cm right para aortic lymph node just below the renal hilum, with apparent compression of the IVC [Fig. 1a]. The differential diagnosis for the CT finding included: disease recurrence versus an inflammatory response to a small fiber of a 4x8 gauze or BioGlue used during the IVC repair. Consideration was given to obtaining a PET-CT at this time; however, given that both inflammatory and neoplastic processes may be FDG avid, decision was made to proceed with a biopsy (Altini et al., 2020).

A CT-guided biopsy was obtained, with histologic examination revealing fragments of smooth muscle, chronically inflamed fibrocollagenous tissue, scant adipose tissue and cores of eosinophilic, acellular "gel-like" material [Fig. 1b and Fig. 1c]. There was no definitive evidence of lymph node tissue and no evidence of carcinoma.

Given the negative biopsy, and that the patient was asymptomatic without other evidence of disease, the decision was made to proceed with observation. Repeat imaging three months later showed a stable lesion measuring 2.8 × 2.4 × 3 cm. The patient has remained clinically stable without evidence of recurrence for eight years.

3. Case 2

A 66 y/o female with biopsy proven high grade endometrial adenocarcinoma underwent a robotic-assisted staging procedure, which was complicated by a puncture injury to IVC during the para-aortic lymph node dissection. The bleeding was controlled with pressure

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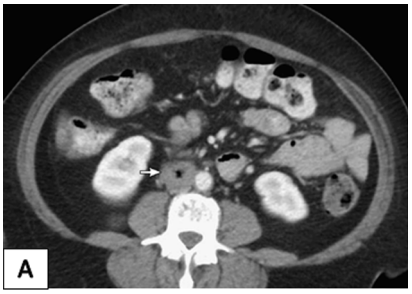

Fig. 1a. CT Abdomen and Pelvis, coronal view, demonstrating a 2.9 × 1.7 × 2.9 cm soft tissue mass with 0.6 cm central hypodense component, compatible with gas, compressing the SVC (White Arrow).

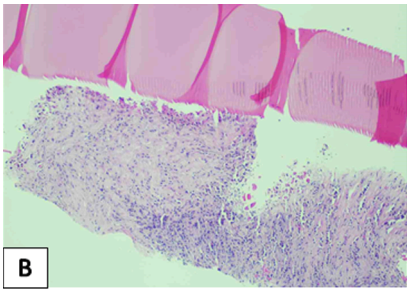

Fig. 1b. CT-guided core needle biopsy of right retroperitoneal mass. Fragment of fibrous tissue with chronic inflammation; abundant acellular eosinophilic proteinaceous material.

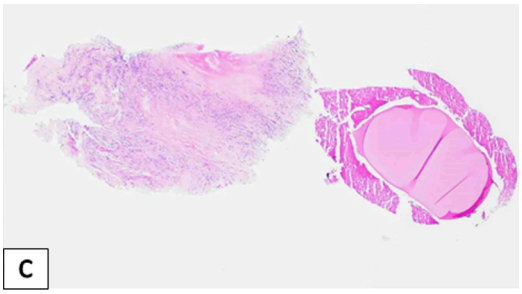

Fig. 1c. CT-guided core needle biopsy of right retroperitoneal mass. Fragment of fibrous tissue with chronic inflammation and fragment of acellular eosinophilic proteinaceous material.

applied with a Ray-Tec gauze, followed by primary repair with a #5-0 vicryl suture in a figure-of-eight fashion. BioGlue™, was also applied to the puncture site after the suture was secured and hemostasis was achieved. The final pathologic diagnosis was a Stage IA uterine carcinosarcoma. The patient was managed postoperatively with adjuvant chemotherapy and radiation.

Fifteen months following the initial surgery, the patient presented to the office with a newly palpable mass in the abdominal wall. A computed tomography (CT) scan of the abdomen and pelvis demonstrated a solid mass in the subcutaneous tissue of abdomen, as well as a right anterior mesenteric nodule, and a stable 4.6 × 3.4 × 5.3 cm heterogeneous mass in the anterior paracaval region causing compression of a patent IVC [Fig. 2a]. The paracaval mass had previously measured 3.2 × 1.6 × 3.1 cm on a CT scan performed nine months prior, after completion of her adjuvant chemotherapy and radiation. Given the experience with case 1 and the relative stability in size, the paracaval mass was suspected to be a sequelae of the hemostatic agent used at the time of IVC injury repair.

The patient subsequently underwent a successful secondary

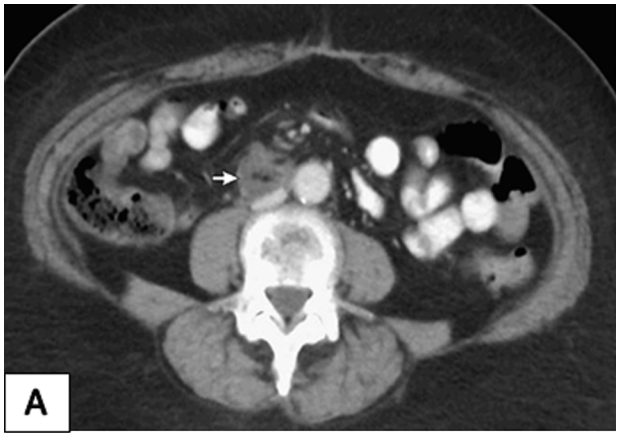

Fig. 2a. CT Abdomen and Pelvis with IV contrast. 4.6 × 2.6 × 2.1 cm. mass with 1 cm central low attenuation central component compressing the anterior wall of the SVC (White Arrow).

debulking of the areas of concern. On histologic examination, the abdominal wall mass and rectus muscle mass were consistent with recurrent carcinosarcoma. Intraoperatively, the paracaval mass was intimately attached to the Vena Cava, requiring meticulous dissection for a complete resection [Fig. 2b]. The gross appearance of the paracaval mass was a combination of fibrinous material and old blood, with no evidence of carcinoma. Sectioning of the paracaval mass revealed a moderate amount of gelatinous hemorrhagic material admixed with tan white fiber-like material on gross examination. No fragments of Ray-Tec gauze were identified. On histologic examination, the paracaval mass was noted to be comprised largely of cystically dilated fibroconnective tissue with scant residual lymphoid tissue containing necrosis and centrally-located acellular, eosinophilic proteinaceous material [Figs. 2c, 2d]. The tissue was negative for malignancy.

4. Discussion

There is variation in the degree of inflammatory response to BioGlue™ in its surgical applications. Hewitt et al, examined histologic specimens from sheep models after aortic grafts with use of BioGlue™ for repair at three months post-procedure. At that time, they reported a "relative paucity of profound inflammatory response," with granulomatous inflammation in only a few specimens (Hewitt et al., 2001). In response, Erasmi and Sievers reported a case of a 10 × 2 × 0.5 cm glue remnant at the time of a re-operation for an aortic aneurysm three months after the initial procedure. Histologic examination

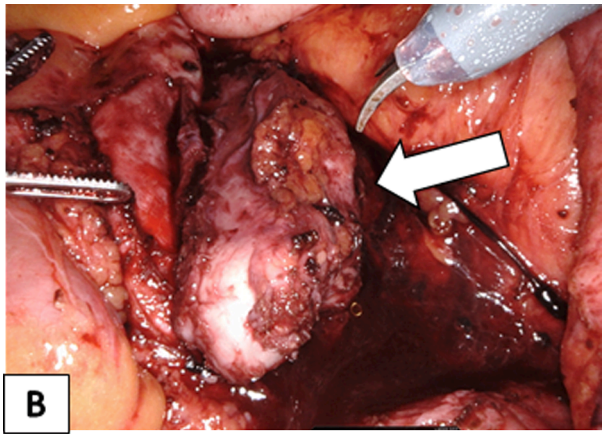

Fig. 2b. Intraoperative image of right paracaval mass (White Arrow) prior to resection, which was intricately attached to the inferior vena cava.

Fig. 2c. Excision of right *para*-aortic mass. Cystic structure; thick, fibrous wall with chronic inflammation and cystic space containing acellular eosinophilic proteinaceous material and necrotic debris.

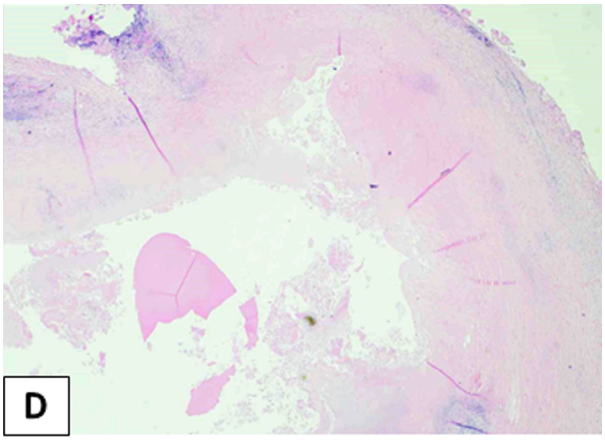

Fig. 2d. Excision of right *para*-aortic mass. Acellular eosinophilic proteinaceous material with necrotic debris.

demonstrated severe active inflammation surrounding the glue remnant with multiple granulocytes, histiocytes, and a massive foreign-body reaction with numerous multinucleated giant cells (Erasmi et al., 2002).

Pathology reports of cases of foreign body reactions to BioGlue™ in the literature have shown granulomatous foreign body type response with macrophages containing tiny droplets of eosinophilic BioGlue™ (Ironside et al., 2018). The pathologic findings in the cases described herein are consistent with these descriptions of foreign body reaction. The biopsy in Case 1 demonstrated chronic inflammation surrounding cores of an eosinophilic acellular "gel-like" material. Case 2 had fibroconnective tissue with lymphoid tissue surrounding acellular proteinaceous material, compatible with BioGlue™. In the absence of retained fibers from a Ray-Tech gauze, it is likely that this finding represents a foreign body reaction to BioGlue™.

From an oncologic perspective, it is problematic that such an inflammatory response could mimic a cancer recurrence. The CT appearance of various other hemostatic agents such as Surgicel™, a hemostatic agent composed of oxidized cellulose, and its mimicry of cancer recurrence has been described in the literature (Morani et al., 2018; Wang and Chen, 2013). CT scans generally will show mixed or low attenuation masses containing focal central collections of gas with faint enhancement at the tumor periphery (O'connor et al., 2003). In foreign body reactions a subsequent FDG-PET/CT scan will generally reveal hypermetabolic nodules with, classically, a rim-shaped uneven FDG-uptake pattern at the periphery of the lesion. While there may be radiographic evidence that suggests a foreign body reaction, there isn't a clear way to differentiate this reaction from a neoplastic process. Furthermore, there is a paucity of data on the use of BioGlue, particularly in oncologic surgical applications. Without a way to differentiate between these processes radiographically, this necessitates biopsy or surgical resection to determine the etiology of the radiographic finding, as evidenced by the two cases presented here. Furthermore, when faced with similar radiologic finding, one should consider review of the operative report to ascertain any clues that may explain similar findings.

There is some evidence to suggest that alternative vessel sealants may be less inflammatory than glutaraldehyde-based solutions. Namely, COSEAL, which is a tetra-succinimidyl and tetra-thiol-derivatised PEG species, may result in less inflammatory cell infiltration and low levels of lymphocytes, plasma cells and B cells in a rabbit model (Slezak et al., 2020). Further investigation is needed to determine whether this translates into human subjects, and whether there is any clinical benefit in terms of reducing inflammatory collections. With the use of sentinel node assessment in surgical treatment of most uterine cancer, the incidence of injury to these major vessels should also be lessened.

5. Conclusion

BioGlue™ is a surgical adhesive that has the potential to cause a foreign body reaction. In the setting of patients with a history of malignancy, this may raise concern for tumor recurrence, leading to additional invasive procedures and workup.

Based on the cases presented here, it is important to note any use of BioGlue™ or other sealant when surveilling a patient post-operatively and to keep a granulomatous reaction on the differential in the case of an isolated *para*-aortic recurrence on imaging studies. It may be reasonable to manage isolated lesions in these cases conservatively, with serial imaging, rather than immediate biopsy. Of course, in the case of multi-site recurrence or high-risk histology, a high index of suspicion for recurrence should be maintained. More investigation is needed to determine the least inflammatory vessel sealants and to better characterize the imaging characteristics of inflammatory collections.

Author Contributions

AF – data procurement, writing of original draft
OK – conceptualization, editing of manuscript
JD – preparation and analysis of radiology slides
TH – preparation and analysis of pathology slides, editing of manuscript and pathologic descriptions
MG – preparation and analysis of pathology slides
DK – conceptualization, resources, editing, supervision.

Declaration of Competing Interest

There are no conflicts of interest to disclose for any of the listed authors.

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