Avitene Granulomas of Colonic Serosa*

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ABSTRACT

Avitene, microfibrillar collagen hemostat, is an absorbable topical hemostatic agent prepared from purified bovine corium collagen. A case is reported of a 58-year-old man who, one month after sigmoid colectomy for volvulus in which Avitene was used to control bleeding from a splenic capsular tear, developed symptoms of intestinal obstruction. On exploratory laparotomy, the transverse and descending colon had numerous 0.1 to 2.0 cm nodules, adherent to the serosa of the bowel and mesentery, with kinking and partial obstruction of the splenic flexure. Light microscopically, the nodules were found to be composed of chronic inflammatory and granulomatous reaction with numerous deposits of eosinophilic fibrillar material consistent with Avitene. Electron microscopic examination of the lesions and of Avitene confirmed the nature of this material. The practical and pathobiological implications of utilization of Avitene as a hemostatic agent are discussed.

Introduction

Avitene, microfibrillar collagen hemostat, is an absorbable topical hemostatic agent prepared as a dry, sterile, fibrous, water insoluble partial hydrochloric acid salt of purified bovine corium collagen.2,5,12 This substance, when in contact with a bleeding surface, attracts platelets which adhere to the fibrils and undergo the release phenomenon to trigger aggregation of platelets into thrombi in the interstices of the collagenous mass.7 Avitene is indicated for use in surgical procedures as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.6,12,14 It has been found especially useful in controlling generalized bleeding from raw or friable tissues, bleeding from highly vascularized organs, bleeding from cancellous bone, and bleeding around vascular anastomoses.
The case reported here is an unusual example of intestinal obstruction caused in part by reaction to Avitene. This microfibrillar collagen hemostat had been used one month previously during surgery on this patient to control bleeding from a small splenic capsular tear. Pathologically, the cause of the marked foreign body granulomatous reaction, chronic inflammation and fibrosis in the colonic serosa was determined by light and electron microscopic study of the colonic serosal lesions, in comparison with light and electron microscopic study of commercially available Avitene.

Case History

The patient was a 58-year-old black male. One month prior to admission, he had a reduction of sigmoid volvulus and a sigmoid colectomy with end-to-end colocolostomy. During this procedure, a small splenic capsular tear had been noted, and bleeding from this tear had been successfully controlled with Avitene and pressure. The Avitene had been applied with forceps and packed with a sponge. On the day of admission the patient developed acute onset of abdominal pain and vomiting. Physical examination demonstrated moderate abdominal distention with tenderness on pressure and hyperactive bowel sounds. Upright abdominal x-ray showed distention of small bowel loops.

Exploratory laparotomy was performed, and two problems were identified. Firstly, the ascending colon was attached by adhesions to the sigmoid colon anastomotic region resulting in an internal hernia and consequent small bowel obstruction; these adhesions were taken down, and one was biopsied. Secondly, the mid-transverse to mid-descending colon had numerous 0.1 to 2.0 cm nodules, adherent to the serosa of the bowel and mesentery, with kinking and partial obstruction of the splenic flexure. Three of these nodules were biopsied. The splenic capsular tear was noted to be well healed. Postoperative course was uneventful and the patient was discharged three weeks after surgery free of abdominal or gastrointestinal symptoms. There has been no further evidence of intestinal obstruction during the subsequent four years.

Materials and Methods

Specimens for light microscopic study, including portions of one ascending colonic adhesion, three splenic flexure nodules, and commercially obtained Avitene, were fixed in formalin, routinely processed for histologic sectioning and stained with hematoxylin-eosin, Masson’s trichrome, phosphotungstic acid-hematoxylin, and periodic acid Schiff (PAS).

Specimens for electron microscopic study, including portions of ascending colonic adhesion, splenic flexure nodules, and commercially obtained Avitene, were fixed in four percent glutaraldehyde in 0.1 M phosphate buffer at pH 7.4. These were postfixed in one percent osmium tetroxide in 0.1 M phosphate buffer, routinely processed, and embedded in epoxy resin. Ultrathin sections were stained with a saturated solution of uranyl acetate and lead citrate and examined in an electron microscope.

Results

GROSS PATHOLOGY

The specimen consisted of three ovoid nodules of soft tissue and one irregular elongated piece of soft tissue (figure 1). The three ovoid nodules (obtained from transverse colonic serosa) measured 2 × 1 × 1 cm, 1.5 × 1 × 1 cm, and 0.9 × 0.6 × 0.5 cm in greatest dimensions. They had an irregular mottled pale reddish brown and yellow external surface, and a rubbery homogeneous pale tan cut surface. The one elongated nodule (obtained from the sigmoid colon anastomotic region) measured 1.3 × 0.5 × 0.4 cm and was similar in color.

LIGHT MICROSCOPY

Hematoxylin-eosin stained sections of the three transverse colonic specimens (figures 2, 3, and 4) showed serosal adipose tissue extensively involved by large and small nodular proliferations of fibrous tissue with moderate to marked chronic inflammatory cell infiltrate and numerous small and large deposits of eosinophilic material frequently asso-
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associated with foreign body giant cells. The inflammatory cell infiltrate was mainly composed of eosinophils with interspersed plasma cells, lymphocytes and histiocytes. The eosinophilic material was variably amorphous and coarsely fibrillar and occurred as minute to large irregular accumulations. The color of this material varied from intensely eosinophilic (similar to normal collagen) to less eosinophilic to somewhat pale gray and faintly basophilic. The more intensely eosinophilic areas tended to appear blue on trichrome stain and under polarized light to have a pink birefringence similar to normal collagen, while the less eosinophilic areas tended to lack these collagenous characteristics. No fibrin was identified in PTAH-stained sections.

Hematoxylin-eosin stained sections of the sigmoid colon anastomotic specimen showed serosal adipose tissue extensively involved by fibrosis with scattered capillaries, patchy recent hemorrhage, minimal focal lymphocytic infiltrate and one suture granuloma. The intercellular material in this specimen consistently demonstrated a blue color on trichrome stain and pink birefringence under polarized light, typical of normal collagen.

Hematoxylin-eosin stained sections of commercially available Avitene (figure 5) showed material similar to that seen in the transverse colonic specimens, except that it was less amorphous and more consistently composed of thick strands of intensely eosinophilic material and narrow coarse fibers of less intensely eosinophilic material with a faintly basophilic hue. This material focally stained blue with trichrome stain and the thick intensely eosinophilic material showed a pink birefringence under polarized light.

**Electron Microscopy**

On electron microscopic study (figures 6, 7, and 8), the transverse colonic granulomatous lesions were found to be mainly composed of histiocytes with scattered eosinophils and occasional lymphocytes. The histiocytes generally had a moderate to marked increase in rough endoplasmic reticulum. The most notable feature of the lesions, however, was the numerous small and large irregularly shaped accumulations of electron dense material, which was adjacent to, partially engulfed by and occasionally phagocytized by the histiocytes. This material was composed of regular cylindrical, moderately electron dense fibers, approximately four times the diameter of typical collagen, within a small amount of highly electron dense matrix.

Ultrastructural study of commercially obtained Avitene (figure 9) demonstrated it to be composed of two main forms of fibrillar material: (1) discrete bundles of cylindrical parallel fibers about four times the diameter of normal collagen, on cross section having a dark central core and pale outer layer and on longitudinal section having a periodicity much finer than that of normal collagen; and (2) loosely arranged cylindrical fibers, similar to those composing the above discrete bundles except for being more electron-dense and less parallel in arrangement. There was focal transition between the discrete bundles of fibers and the loosely arranged fibers. The fibrillar material which had been seen

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**Figure 1.** External (a) and cut (b) surfaces of three nodules removed from transverse colonic serosa. The fourth tissue (lower right) is fibrous tissue removed from sigmoid colon anastomotic region.

**Figures 2, 3 AND 4.** Medium, low, and high power views of nodule from transverse colonic serosa. Multiple irregular deposits of amorphous and coarsely fibrillar material are dispersed about fibrous tissue with granulomatous reaction and chronic inflammation.

**Figure 5.** High power view of section of commercially available Avitene, similar in appearance to the material in figure 4.
Figures 6, 7, and 8. Electron microscopic appearance of nodule from transverse colonic serosa. Histio­cytes with prominent rough endoplasmic reticulum are associated with intracellular and extracellular deposits of cylindrical fibrillary material. The fibers have a diameter approximately four times that of typical collagen. (Figure 6, × 2810; figure 7, × 8960; figure 8, × 14180).

Figure 9. Electron microscopic appearance of commercially available Avitene. The fibers have dimensions similar to those in figures 7 and 8, but also have some features of typical collagen fibers. (× 8820).
in the pericolonic granulomas was similar to the loosely arranged fibers of Avitene, except for the former fibers being embedded in a small amount of highly electron-dense matrix and having a finely microfibrillary texture with very little evidence of periodicity on longitudinal section. The previous findings were felt to be consistent with the conclusion that the pericolonic granulomas represented a foreign body reaction to Avitene.

Electron microscopic study of the sigmoid colonic anastomotic specimen (pericolonic fibrotic area separate from the transverse colonic granulomas) demonstrated reactive fibrocyte proliferation and collagen deposition. The collagen fibers were typical in diameter and periodicity and had a diameter about four times less than Avitene and the material in the granulomas. This was felt to indicate that the nature of the collagenous material composing Avitene (and the material in the transverse colonic granulomas) was different from normal collagen present in the patient's sigmoid pericolonic fibrosis.

Discussion

Inadvertant splenic laceration is a common complication of left upper quadrant surgery, and this has frequently been successfully treated by the topical application of Avitene\textsuperscript{9,10}, as in the case reported here. Adverse reactions to Avitene have been reported, and the most serious of these appear to be potentiation of infection (abscesses, etc.), hematoma and wound dehiscence. Other reported adverse reactions include allergic responses, adhesions and foreign body reactions.\textsuperscript{3,11,13,14} These last three, particularly foreign body reaction, appear to have been involved in the present reported case. In one reported series of 811 patients treated with Avitene, there were 103 instances of adverse responses, including two with foreign body reactions and three with adhesions.\textsuperscript{14} Thus it can be seen that such complications are relatively infrequent.

The cause of the unexpected adverse response to Avitene which occurred in this case is difficult to ascertain exactly but is likely related to several factors such as immunologic reactivity and intraoperative technique. Immunologic hyperreactivity is suggested by the marked infiltration of eosinophilic leukocytes involving all of the biopsied Avitene granulomas. Such an eosinophilic infiltrate has not been reported to be characteristic of the usual local tissue response to Avitene,\textsuperscript{15} or, for that matter, to other injectable bovine collagen preparations.\textsuperscript{1} This peculiar response in the present case appears to represent a local manifestation of a systemic immunologic response since review of the patient's laboratory data revealed that his peripheral blood eosinophils increased from zero to one percent at the time of the first surgery and Avitene treatment to five to 15 percent one month later. The few apparent allergic reactions to Avitene reported in patients have simply consisted of erythema or pruritis.\textsuperscript{14} Furthermore, extensive immunologic studies in animals (guinea pigs, rabbits and dogs) and humans have indicated that allergic reactions to Avitene should be rare and of little significance. It is unknown why the patient reported here had developed an immunologic reactivity which apparently resulted in the local and systemic eosinophilia.

Another cause of the unexpected adverse reaction to Avitene which occurred in this case was likely related to the technique involved in Avitene application. The numerous nodules noted during the second operation were adherent to the serosa and mesentery from mid-transverse to mid-descending colon. This would indicate a more extensive
application of Avitene than was required to treat the splenic capsular tear, perhaps in part due to colonic serosa and mesentery inadvertently coming into contact with the site of splenic application. The prevention or lessening of the occurrence of this problem appears to now be available, with the development of a method of preparing Avitene into a discrete firm pledget using a syringe.4

One important aspect of this case involves the identification of a material which appears to be eliciting a foreign body granulomatous reaction. References such as the excellent Particle Atlas8 are one available approach but in the present case were of little help in solving this problem. In this case the steps which yielded the identification of the material included: (1) review of the operative report and communication between the pathologist and surgeon, resulting in information which circumstantially incriminated Avitene; (2) light microscopic examination with routine and special stains, comparing the patient’s biopsy material with commercially available Avitene; and (3) electron microscopic examination, comparing the patient’s biopsy material and Avitene.

In summary, Avitene (microfibrillar collagen hemostat) can be a highly beneficial agent as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical. Surgeons, however, should be aware of potential complications, which in the present case were probably related to immunologic reactivity and operative technique. Furthermore, pathologists should be aware of the histomorphologic appearance of this material which may result in bowel obstruction and other complications.

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References