

Foreign-Body Granulomas within Intramyocardial Arteries in a Transcoronary Safety Assessment in Pigs

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ABSTRACT

Foreign-body granulomas within intramyocardial arteries were detected in three domestic pigs (*Sus scrofa domestica*) in a routine transcoronary safety assessment study. The foreign bodies stained light grayish-blue by hematoxylin and eosin (H&E) and were strongly birefringent by polarized light microscopy. By their morphological features, they were identified as cotton fibers. Embolization of foreign-body material into the myocardial arteries following catheter-based procedures is an unusual event, and its occurrence may lead to granulomatous foreign-body reaction and misinterpretation of histological results.

Keywords: granuloma; foreign body; embolization; coronary; angiography.

Only a small number of cases of foreign-body embolization in cardiac arteries following catheter-based procedures have been reported (Fischi and Narins 2005). The observance of subsequent granulomatous reaction may present a diagnostic challenge, especially in drug safety studies, and may lead to incorrect conclusions drawn from histological data. In the present report we describe the occurrence of granulomatous reaction to cotton gauze fragments following coronary intervention in three domestic pigs (*Sus scrofa domestica*).

Five 3- to 4-month-old female domestic pigs, weighing 45–50 kg, were assigned to the intervention group of an eight-day intracoronary toxicity study. Before the beginning of the trial, the gilts were physically examined for signs of ill health and found fit to participate in the study. The animals were operated on in the Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, Israel, and hospitalized in The Institute of Animal Research, Kibbutz Lahav, Israel (inside a special holding room). The gilts were examined twice daily for their clinical status. Animal handling was conducted in accordance with guidelines of the National Institutes of Health (National Research Council 1996). The study was approved by the institu-

tional Ethical Committee for Animal Research of Sheba Medical Center and the Tel Aviv University, Tel Aviv, Israel.

On day 0 of the study, after appropriate premedication with intramuscularly administered ketamine and xylazine and intravenous administration of diazepam, intubation was performed after induction with isoflurane via a face mask. Maintenance of anesthesia was achieved using isoflurane. After the animals were properly anesthetized, they underwent catheterization of the left anterior descending coronary artery via the left subclavian artery using the Seldinger technique. Positioning of the catheter was assessed by administration of a nonionic contrast medium. A balloon was inflated under low pressure for sixty minutes to induce myocardial infarction. This procedure was followed by angiography of the coronary vessels. On day 3, a second catheterization was performed, and the test material was injected into the infarcted area. The chemical nature of the tested compound is irrelevant, as the described lesions were associated with inadvertent foreign-body injection related to the technical procedure. This injection was followed by injection of 2 mL of saline and, subsequently, coronary angiography.

On day 8, animals were sacrificed with an overdose of KCl and subjected to thorough examination of the external surface of the body; all orifices; and cranial, thoracic, and abdominal cavities and their contents. Liver, thymus, spleen, mesenteric lymph nodes, kidneys, brain, bone (femur), and heart tissues were preserved

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in 4% formaldehyde solution and processed for histological examination. Tissues were trimmed, embedded in paraffin, sectioned at a thickness of approximately 5 microns, and stained with H&E. We report only the findings from the heart. Samples from the left and right atria and left, right, and interventricular walls were trimmed. Selected sections were stained by Ziehl Neelsen (used as a diagnostic staining for the hair shaft) and mouse anti-human pancytokeratin antibodies (Zymed Laboratories, Inc., San. Francisco, CA, USA, 1:100 dilution).

In three out of five animals in the transcortary safety testing group, several intramural foreign-body granulomas were noted within the lumena of intramyocardial arteries. The granulomas were partially occlusive, and in some cases the inflammation extended beyond the adventitia. The granulomatous inflammation consisted mainly of histiocytes, multinucleated giant cells, fibroblasts, and a small number of polymorphonuclear cells, associated with the presence of foreign bodies engulfed by the giant cells. No granulomas or foreign body material were seen in any of the other organs histologically evaluated.

The foreign-body emboli consisted of hollow oval and U-shaped rings. The material was either unstained or stained light grayish-blue by H&E (Figure 1A), did not stain with Ziehl Neelsen or pancytokeratin, and was strongly birefringent by polarized light microscopy (Figure 1B). This appearance is typical of cotton fiber, as may be seen in cotton gauze swabs and cotton sutures (Yeh et al. 1997). Possible contamination during histological processing with textile fibers as a secondary factor can be excluded owing to the presence of cellular reaction to the foreign material. We suggest, therefore, that the foreign material consisted of fragmented fibers of cotton gauze, inadvertently introduced during the transcortary intervention.

Granulomas appearing in tissues and blood vessels may originate from a variety of causes and present a possible diagnostic challenge. This inflammatory response may be a manifestation of many infective, toxic, allergic, autoimmune, and neoplastic diseases, as well as conditions of unknown etiology (Williams and Williams 1983). Granulomatous inflammation, resulting from drug therapy, has been described in different organs and can be found mainly in the skin, but also in the liver and kidney (Magro et al. 1998). Thus, careful assessment of the origin of the granulomatous inflammation is of utmost importance in toxicological studies.

Foreign-body embolization, appearing rarely in clinical and experimental studies, includes embolization of gaseous materials developing within the female genital tract during labor or abortion or originating from needles or vascular lacerations (Cina et al. 1994). Other iatrogenic emboli reported to be introduced by intravenous injections include hair fragments, epidermal cells, corn starch, cellulose particles, and asbestos (Yamamoto et al. 1982). Iatrogenic emboli may also originate from shearing off of catheter tips during intravascular cannulation (Doering et al. 1967; Ross 1970); silicone emboli have developed after injection for cosmetic alterations (Rodriguez et al. 1989; Solomons and Jones 1975). Penetrating trauma is another cause for foreign-body emboli, with a variety of sources reported, including missiles, pins, and zippers (Cina et al. 1994).

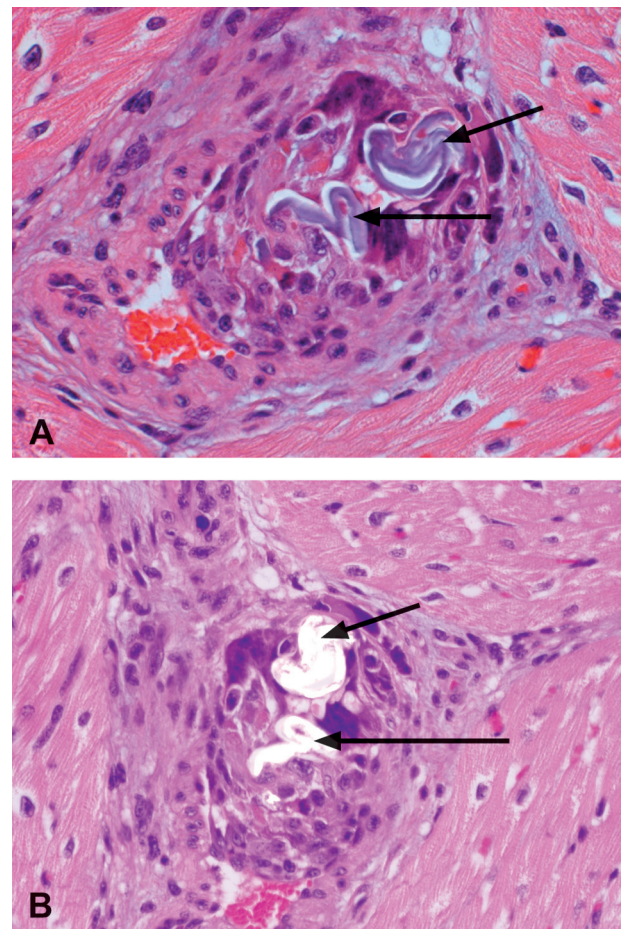


FIGURE 1.—(A), (B) Partially occluding intra-arterial foreign-body granuloma in left ventricle of pig subjected to transcortary intervention. Arrows indicate cotton-gauze foreign body. (A) Note multinucleated giant cells. Hematoxylin and eosin. X40. (B) Cotton fibers show birefringence by polarized light microscopy. x60.

Embolization of cotton fibers in the human vascular system has been described, and intra-arterial cotton-fiber granulomas have been reported in different locations, causing cerebral, renal, and pulmonary infarcts. Coronary cotton emboli have been reported following heart surgery (Tubbs et al. 1980).

Although delivery of foreign material into the coronary circulation during transcortary interventions is rare, embolization of angiographic equipment, such as catheters, guidewires, balloon fragments, and stents, has been reported. One case report described embolization of gauze during coronary angiography in a forty-four-year-old woman (Fischi and Narins 2005).

In a preclinical stent investigation in pigs, cross sections of stented coronary arteries were studied histologically. A total of 19.6% of the animals showed starch materials, and 6.5% exhibited textile fiber contamination. Contamination of instruments with textile fibers, most probably gauze, during the implantation procedure was implicated. The fibers likely adhered to the guidewire, stent, or balloon and were carried into the vessel, lodging in its wall; their deposition has resulted in granulomatous formation. Gauze fibers are known to persist for several

weeks after implantation and thereby lead to a long and persistent foreign-body reaction (Whelan et al. 1997). Although additional investigation is necessary, our study suggests that gauze contamination may occur at a higher prevalence than previously thought. It may not be associated exclusively with stent placement but may occur in other kinds of transcatheter interventions as well.

We have described the occurrence of incidental myocardial intravascular foreign-body granulomas observed in three study pigs. This observation emphasizes that foreign-body embolization can occur during invasive vascular interventions, which may lead to foreign-body reaction and misinterpretation of drug safety results. When assessment of drug safety is performed during an intracardiac intervention, this possibility should be taken into consideration. During the study, appropriate measures should be applied to reduce the chances of contamination.

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