Stent hypersensitivity and infection in sinus cavities

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ABSTRACT
Persistent mucosal inflammation, granulation tissue formation, hypersensitivity, and multifactorial infection are newly described complications of retained drug-eluting stents from endoscopic sinus surgery for refractory rhinosinusitis. In an important report published in Allergy and Rhinology, a 45-year-old male patient suffering from recalcitrant chronic rhinosinusitis underwent functional endoscopic sinus surgery and was found, for the first time, to have steroid-eluting catheters that were inadvertently left in the ethmoid and frontal sinuses. The retained catheters had caused persistent mucosal inflammation and formation of granulation tissue denoting hypersensitivity reaction. These consequences had induced perpetuation of symptoms of chronic rhinosinusitis. Meticulous removal of the retained stents with the nitinol wings from inflamed tissues of the frontal, ethmoidal, and sphenoid recesses in which they were completely imbedded was successfully performed without polypoid regrowth. Cultures of specimens taken from both left and right sinuses showed heavy growth of Stenotrophomonas maltophilia and moderate growth of Klebsiella oxytoca, coagulase negative Staphylococcus, and beta-hemolytic Streptococcus anginosus. Fungal infection was not detected. The current knowledge and experience regarding stent hypersensitivity and infection in relation with the use of stents in sinus cavities is reviewed.

(Allergy Rhinol 4:e162–e165, 2013; doi: 10.2500/ar.2013.4.0071)

STENT COMPONENTS AND HYPERSENSITIVITY
So far, drug-eluting stents are composed from the metal strut, which is made from stainless steel that contains nickel, chromium, manganese, titanium, and molybdenum, the polymer coating and the eluted drugs that vary from corticosteroids, as in the described patient, to different antiproliferative and antineoplastic agents. The latter include paclitaxel, rapamycin, zotarolimus, everolimus, biolimus, tacrolimus, pimecrolimus, etc. All of these components are strong antigens and constitute an allergic complex inside the affected tissue, which applies continuous, persistent, and repetitive antigen exposure that lasts as long as the antigen is present. Furthermore, any atopic patient with stent implantation, in the real world, is exposed to any environmental risk such as drugs, insect stings, etc. Therefore, more than five antigens, perhaps six, can join forces to degranulate mast cells and release their mediators. We must emphasize that mast cell surface brings 500,000 to 1 million IgE molecules and degranulation occurs when 2000 of these molecules make 1000 bridges by antigens of different specificities as it happens in the stented patients.

Unexpected, bizarre, strange, astonishing, and surprising reports have shown patients who developed stent component hypersensitivity immediately after...
an allergic reaction from other causes. These reports concern mainly stents implanted in the coronary arteries. For example, allergic reactions from propyphenazone,6 contrast material,7 and insect sting8 were accompanied with intrastent hypersensitivity with resulting thrombosis manifesting as Kounis syndrome.9 It seems likely that stents, like magnets, attract inflammatory cells and constitute the area of possible mast cell and platelet activation.

Granulation tissue in and around stented sinus cavities denoting hypersensitivity inflammation have been also described.4 In this report, the mucosal inflammation together with granulation tissue found in the area of ethmoid and frontal sinuses around the retained stents that perpetuated the symptoms of chronic rhinosinusitis may well be the result of hypersensitivity to stent components. Indeed, the stent nitinol wings are made from nickel–titanium alloy and can act as strong antigenic compounds.10 Nickel can induce a variety of allergic reactions including baboon syndrome.9 Similar hypersensitivity reactions can be induced by the polymer coating and the eluted drugs. The described patient,3 in particular, was taking multiple combinations of oral and topical therapies such as prednisone daily, as well as nasal antihistamine spray without resolution of his symptoms. These medications can surprisingly cause hypersensitivity reactions.12,13 Development of granulation tissue with crusting necessitated the removal of a corticosteroid-eluting stent in a patient reported in the ADVANCE II study.14 This study, however, provided a high level of evidence that the use of steroid-releasing implants that apply a sustained release of corticosteroid improves surgical outcomes by reducing synchiae formation, polyposis, and the need for postoperative interventions, with no observable ocular safety risk.14 Therefore, hypersensitivity to implanted stent components, although rare, is an existing possibility and should be always brought to mind when symptoms perpetuate after stent insertion and despite application of appropriate medical therapy. Bioabsorbable, allergy-free, poly lactic acid self-expanding stents and nickel-free stainless steel stent materials15 in combination with balloon dilatation1 may provide an interesting and minimally invasive future development. These stents would control underlying inflammation and/or hypersensitivity in chronic rhinosinusitis that occurs in conjunction with sinus ostial dilatation.

CORTICOSTEROID-ELUTING STENTS

Corticosteroid-eluting stents are useful after endoscopic sinus surgery in maintaining sinus patency and reducing inflammation.18 Corticosteroids can suppress the release of arachidonic acid from cell membrane and inhibit eicosanoid biosynthesis. The suppression of arachidonic acid release, especially from mast cells, is mediated through the inhibition of phospholipase A2. Corticosteroids, through reduction of the transcription of several proinflammatory cytokines, including C-reactive protein, can reduce the risk of allergy.9 Experiments in pigs with methylprednisolone-eluting stents have shown that both vascular macrophage infiltration and instent neointimal hyperplasia could effectively be decreased.20 Other experiments with phosphorylcholine-coated stents eluting methylprednisolone have shown that inflammatory response and thrombus formation could effectively be decreased.21

Improvement in the clinical and angiographic outcomes when compared with the control stents has been achieved with dexamethasone.22 Dexamethasone-eluting stents are associated with reduced plasma concentration of intercellular adhesion molecule 1 and vascular cell adhesion molecule 123 and lower adverse events during follow-up.24 High doses of dexamethasone-loaded stents do not significantly reduce neointimal hyperplasia and can induce morphological changes pointing to a loss of vascular integrity.25

In studies concerning the coronary arteries, dexamethasone-eluting stents used in patients with diabetes mellitus have shown that the restenosis rate is higher, suggesting that stent restenosis is unlikely to be related to decreased acute systemic inflammation but to an increased local resistance to inflammatory mediators.19

In the field of otolaryngology, experiments with an ethylene vinyl acetate steroid-delivering stent in an animal model have confirmed the benefit of steroids on sinus wound healing. Indeed, comparison of a silicone
stent to a dexamethasone drug-eluting stent, providing 30 days of continuous steroid release, revealed that the drug-eluting stent induced less macroscopic granulation and thinner epithelial stroma.25

In chronic rhinosinusitis a biodegradable polymer in a lattice-pattern stent has been recently developed to dilate and deliver topical steroids to the postoperative sinus cavities.1 The stent polymer matrix is impregnated with mometasone furoate, which is a glucocorticosteroid and constitutes the prodrug of the free-form mometasone. As a scaffold, the stent maintains medi-alization of the middle turbinate and prevents the development of scarring between the middle turbinate and the lateral nasal wall. Mometasone furoate is highly lipophilic and has been shown to reside in mucosal tissue for up to 60 days after stent placement. An average of 15% of stent material is present by day 30 and decreases to 0.2% after 60 days, showing successful absorption of the stent.26

The efficacy of this stent has been studied in three major studies so far. In the first study it was found to provide statistically significant reductions in postoperative inflammation, polyp formation, and the need for systemic steroids in the first 30 postoperative days.27 In the second study this stent provided minimal mean ethmoid sinus inflammation scores and low rates of polypoid tissue formation, adhesion formation, and middle turbinate lateralization.26 In the third study this stent provided a 29.0% relative reduction in postoperative interventions, a 52% decrease in necessary lysis of adhesions, and a 44.9% relative reduction in frank polyposis.28 In these studies, one patient with crusting and granulation tissue formation required removal the stent, another patient experienced infection of the contralateral sinus after removal of the control stent, and a third patient complained of worsening of the sensation of sinus pressure and irritation, which attributed to crusting adherent to the stent. This stent is currently undergoing investigation for the postoperative ethmoid sinus cavity. Future application of such stents as well as other new stents impregnated with antibiotics and other anti-inflammatory agents could be used to conform to frontal, sphenoid, and/or maxillary sinuses. It seems that the stent era has already invaded in the field of otolaryngology.

STENTS FOR SINUS CAVITIES AND BEYOND

Although coronary arteries and other arterial stenoses are the sites for stent implantation and coronary stent implantation has become the most frequent performed therapeutic procedure,29 stents are also very helpful in other areas of the human body, especially in sinus surgery because they can maintain sinus patency and relieve symptomatology. They have been used in many otorhinolaryngological procedures, in gastric outlet obstructions, pancreatobiliary tract obstructions, for prevention of postendoscopic retrograde cholangiopancreatography pancreatitis, oesophageal leaks, stenotic complications after tracheal resection, intes-tinal stenoses, postoperative intraabdominal and pelvic fluid collections, and, recently, for retinal detachment.30

Chronic rhinosinusitis is characterized by inflammation of the mucosa of the nose and paranasal sinuses. Although the etiology of chronic rhinosinusitis is still unclear, many causes have been incriminated. These include anatomic variations, environmental and genetic factors, superantigens, atopic response, immunodeficiency, biofilms, disturbances in mucociliary clearance, fungal stimulation, and microbial colonization.1 Functional endoscopic sinus surgery has proved effective for both maintaining the flow pathways and topical delivery of drugs.31 Stents are used to fulfill the aforementioned purposes and to avoid complications such as prevent synechial bands or stenosis, prevent space filling with blood, fibrin or mucus, provide matrix for epithelial migration, and act as an occlusive dressing that facilitates would healing.32 Endoscopic sinus surgery for chronic rhinosinusitis may be complicated by postoperative inflammation, polyposis, and adhesions, often requiring subsequent interven-tion. The bioabsorbable stents releasing mometasone furoate have been used to prevent these complications. It has been found that sustained release of corticosteroid improves surgical outcomes by reducing synchiea formation, polyposis, and the need for postop-erative interventions, with no observable ocular safety risk. This opposes the action of dexamethasone-eluting stents observed in the coronary arteries.22 Furthermore, in frontal sinus surgery, which is a challenging procedure, double J stents have been used as frontal sinus stents. They have proved to be self-retaining with no need for sutures, well tolerated by patients, and easily applied.33 Poor postoperative healing after sinus surgery is associated with high concentrations of matrix metalloproteinase 9. Frontal sinus stents have been also used to overcome frontal recess-associated restenosis. In patients suffering from chronic rhinosinusitis, doxycycline-releasing stents, delivering this matrix metalloproteinase 9 synthesis-suppressing agent locally to the frontal recess area adequately suppressed bacterial growth compared with placebo stents. They improved also postoperative healing quality after functional endoscopic sinus surgery.34 Finally, stents have been used for surgical treatment of congenital malfor-mations such as choana atresia. Stenting the choana, the lumen of the stent, provides an airway to facilitate nasal pattern breathing in neonates. Therefore, mainte-nance of the stent lumen patency is extremely impor-tant.35

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CONCLUSION

Today, stents constitute modern devices that are implanted in every area of the human body. Stent implantation is a symptom relieving and lifesaving procedure that has become the most frequently performed therapeutic procedure in medicine. Future research should be directed to prevent stent infection, stent hypersensitivity, and stent stabilization.

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