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 sphenoethmoidal recesses in which they were completely imbedded was successfully performed without polypoid regrowth. Cultures of specimens taken from both left and right stents 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.*

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Stents are implanted in every site of the human body and this procedure has become the most frequently performed therapeutic method in medicine. Bare metal stents, drug-eluting stents, self-expanding stents, and biodegradable self-expanding stents are used for treatment of arterial stenoses, aortic aneurysms, and in sinus surgery because they can maintain sinus patency.[1] Areas of stent implantation beyond coronary, cerebral arteries and carotids include[2] otorhinolaryngological diseases, gastric outlet obstructions, pancreatobiliary tract obstructions, for prevention of postendoscopic retrograde cholangiopancreatography pancreatitis, oesophageal leaks, stenotic complications after tracheal resection, intestinal stenoses, postoperative intraabdominal, and pelvic fluid collections. They have been also used experimentally for the treatment of retinal detachment. Some of their main complications are stent thrombosis, stent restenosis, stent hypersensitivity, and stent migration. In some rare cases stent infection, stent removal, inadvertent stent extraction, and stent retaining may be potential problems. Such a case, with retained steroid-eluting stents causing persistent mucosal inflammation and formation of granulation tissue denoting hypersensitivity reaction was published in *Allergy and Rhinology*.[3] In the following article we present the current literature regarding hypersensitivity to stent components including the pathophysiology of local and systemic responses, other reports of stent infection, and special considerations when the stents elude or are coated with drugs. Future efforts should be focused on prevention of the aforementioned complications and improvement of therapeutic benefits.

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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.*[4] 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.[5]

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 sting[8] 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.[3] 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.[10,11] 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 synechiae 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 materials[15] in combination with balloon dilatation[1] 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.

STENT INFECTION

The implanted and retained stents in the described patient were found to be infected by *Stenotrophomonas maltophilia*, *Klebsiella oxytoca*, coagulase-negative *Staphylococcus*, and β-hemolytic *Streptococcus anginosus* but without fungal infection. Few reports concerning coronary stents have shown that bacteremia after percutaneous coronary intervention occurs in <1% of patients and has largely insignificant clinical sequelae.[16] Similarly, few cases of coronary stent infection with mycotic aneurysm formation have been reported.[17] Any implanted foreign body is susceptible to the development of an infection, but in coronary arteries the high-flow state of blood perhaps prevents an intravascular stent from becoming a nidus of infection. Although the overall incidence of stent infection is unknown, in other areas with slow blood flow state this complication might be increased. Antibiotics and other specific treatment are necessary for stent infection, together with close follow-up, and perhaps surgical intervention to remove the infected and retained stent is mandatory as in the described case.

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 [19] Experiments in pigs with methylprednisolone-eluting stents have shown that both vascular macrophage infiltration and in-stent 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 1[23] 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.[22]

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 medialization 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, intestinal 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 intervention. 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 synechiae formation, polyposis, and the need for postoperative 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 malformations such as choana atresia. Stenting the choana, the lumen of the stent, provides an airway to facilitate nasal pattern breathing in neonates. Therefore, maintenance of the stent lumen patency is extremely important.[35]

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.

REFERENCES

1. Wei CC, and Kennedy DW. Mometasone implant for chronic rhinosinusitis. Med Devices (Auckl) 5:75–80, 2012.
2. Bergström M, Vázquez JA, and Park PO. Self-expandable metal stents as a new treatment option for perforated duodenal ulcer. Endoscopy 45:222–225, 2013.
3. Sjogren PP, Parker NP, and Boyer HC. Retained drug-eluting stents and recalcitrant chronic rhinosinusitis: A case report. Allergy Rhinol (Providence) 4:e45–e48, 2013.
4. Kounis NG, Hahalis G, and Theoharides TC. Coronary stents, hypersensitivity reactions, and the Kounis syndrome. J Interv Cardiol 20:314–323, 2007.
5. Nopp A, Johansson SG, Lundberg M, and Oman H. Simultaneous exposure of several allergens has an additive effect on multisensitized basophils. Allergy 61:1366–1368, 2006.
6. Patanè S, Marte F, Di Bella G, et al. Acute myocardial infarction and Kounis syndrome. Int J Cardiol 134:e45–e46, 2009.
7. Kogias JS, Papadakis EX, Tsatiris CG, et al. Kounis syndrome: A manifestation of drug-eluting stent thrombosis associated with allergic reaction to contrast material. Int J Cardiol 139:206–209, 2010.
8. Greif M, Pohl T, Oversohl N, et al. Acute stent thrombosis in a sirolimus eluting stent after wasp sting causing acute myocardial infarction: A case report. Cases J 2:7800, 2009.
9. Kounis NG, Mazarakis A, Tsigkas G, et al. Kounis syndrome: A new twist on an old disease. Future Cardiol 7:805–824, 2011.
10. Zurawin RK, and Zurawin JL. Adverse events due to suspected nickel hypersensitivity in patients with essure micro-inserts. J Minim Invasive Gynecol 18:475–482, 2011.
11. Rigatelli G, Cardaioli P, Giordan M, et al. Nickel allergy in interatrial shunt device–based closure patients. Congenital Heart Dis 2:416–420, 2007.
12. Calogiuri GF, Nettis E, Di Leo E, et al. Long-term selective IgE-mediated hypersensitivity to hydrocortisone sodium succinate. Allergol Immunopathol (Madr) 41:206–208, 2013.
13. Mitsias DI, and Vovolis V. Anaphylaxis to dimenhydrinate caused by the theophylline component. J Investig Allergol Clin Immunol 21:317–318, 2011.
14. Marple BF, Smith TL, Han JK, et al. ADVANCE II: A prospective, randomized study assessing safety and efficacy of bioabsorbable steroid-releasing sinus implants. Otolaryngol Head Neck Surg 146:1004–1011, 2012.
15. Kounis NG, Giannopoulos S, Tsigkas GG, and Goudevenos J. Eosinophilic responses to stent implantation and the risk of Kounis hypersensitivity associated coronary syndrome. Int J Cardiol 156:125–132, 2012.
16. Baddour LM, Bettmann MA, and Bolger AF. Nonvalvular cardiovascular device-related infections. Circulation 108:2015–2031, 2003.
17. Patel AJ, Mehta RM, Gandhi DB, et al. Coronary aneurysm and purulent pericardial effusion: Old disease with an unusual cause. Ann Thorac Surg 95:1791–1793, 2013.
18. Li PM, Downie D, and Hwang PH. Controlled steroid delivery via bioabsorbable stent: Safety and performance in a rabbit model. Am J Rhinol Allergy 23:591–596, 2009.
19. Gaspardone A, Versaci F, Tomai F, et al. C-reactive protein, clinical outcome, and restenosis rates after implantation of different drug-eluting stents. Am J Cardiol 97:1311–1316, 2006.
20. Wang L, Salu K, Verbeken E, et al. Stent-mediated methylprednisolone delivery reduces macrophage contents and in-stent neointimal formation. Coron Artery Dis 16:237–243, 2005.
21. Huang Y, Liu X, Wang L, et al. Local methylprednisolone delivery using a BiodivYsio phosphorylcholine-coated drug-delivery stent reduces inflammation and neointimal hyperplasia in a porcine coronary stent model. Int J Cardiovasc Intervent 5:166–171, 2003.
22. Hoffmann R, Langenberg R, Radke P, et al. Evaluation of a high-dose dexamethasone-eluting stent. Am J Cardiol 94:193–195, 2004.
23. Patti G, Chello M, Pasceri V, et al. Dexamethasone-eluting stents and plasma concentrations of adhesion molecules in patients with unstable coronary syndromes: Results of the historically SESAME study. Clin Ther 27:1411–1419, 2005.
24. Patti G, Pasceri V, Carminati P, et al. Effect of dexamethasone-eluting stents on systemic inflammatory response in patients with unstable angina pectoris or recent myocardial infarction undergoing percutaneous coronary intervention. Am J Cardiol 95:502–505, 2005.
25. Beule AG, Scharf C, Biebler KE, et al. Effects of topically applied dexamethasone on mucosal wound healing using a drug-releasing stent. Laryngoscope 118:2073–2077, 2008.
26. Murr AH, Smith TL, Hwang PH, et al. Safety and efficacy of a novel bioabsorbable, steroid-eluting sinus stent. Int Forum Allergy Rhinol 1:23–32, 2011.
27. Forwith KD, Chandra RK, Yun PT, et al. ADVANCE: A multisite trial of bioabsorbable steroid-eluting sinus implants. Laryngoscope 121:2473–2480, 2011.
28. Marple BF, Smith TL, Han JK, et al. Advance II: A prospective, randomized study assessing safety and efficacy of bioabsorbable steroid-releasing sinus implants. Otolaryngol Head Neck Surg 146:1004–1011, 2012.
29. Nabel EG, and Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med 366:54–63, 2012.
30. Peng YJ, Lu YT, Liu KS, et al. Biodegradable balloon-expandable self-locking polycaprolactone stents as buckling explants for the treatment of retinal detachment: An in vitro and in vivo study. J Biomed Mater Res A 101:167–175, 2013.
31. Senior BA, Kennedy DW, Tanabodee J, et al. Long-term results of functional endoscopic sinus surgery. Laryngoscope 108:151–157, 1998.
32. Bednarski KA, and Kuhn FA. Stents and drug-eluting stents. Otolaryngol Clin North Am 42:857–866, 2009.
33. Mansour HA. Double J stent of frontal sinus outflow tract in revision frontal sinus surgery. J Laryngol Otol 127:43–47, 2013.
34. Huvenne W, Zhang N, Tijsma E, et al. Pilot study using doxycycline-releasing stents to ameliorate postoperative healing quality after sinus surgery. Wound Repair Regen 16:757–767, 2008.
35. Sattar MA, Hadi HI, Homaira R, and Sultana T. Management of bilateral congenital choanal atresia. Mymensingh Med J 22:80–83, 2013. □