LATE LEFT ATRIAL THROMBOSIS OF AN AMPLATZER PATENT FORAMEN OVALE OCCLUDER MAY BE THE RESULT OF KOUNIS HYPERSENSITIVITY-ASSOCIATED SYNDROME
To the Editor:

In the very interesting report by Klotz and colleagues¹ published in this Journal, a patient with a patent foramen ovale that was successfully occluded with an Amplatzer occluder had a large thrombosis develop on the atrial disk of the device 33 months after the initial implantation. Although Klotz and colleagues¹ did not refer to the etiology of thrombus formation, several such causes have been reported, including incorrect device placement, device size, device instability, anticoagulation, and antiplatelet therapy monitoring.

The Amplatzer closure device is made from nitinol, which is a nickel-titanium alloy. Nickel allergy is quite common, and in a recent report the overall prevalence was found to be 24.6%. Titanium hypersensitivity, although low, has been seen in dental procedures and induces implant failure.² The described patient received also aspirin and warfarin on several occasions, both of which are well-known antigenic compounds.³ It is known that mast cells bring, on their surface, 500,000 to 1 million IgE molecules, and to degranulate they need 2000 of these molecules, which is a critical number, to make 1000

bridges with antigens. These bridges can be made by antigens of different specificities, as happens in patients with metal device implantation. It looks likely that the more antigens to which a patient with metal device implantation, is exposed the more easily and quickly the degranulation occurs.²

Nickel and titanium ions acting as antigens can activate platelets to release proinflammatory, prothrombotic, adhesive, and aggregatory mediators to induce thrombus formation.⁴ Platelet activation is taking place through stimulation of some known receptors in the platelet surface, such as receptors for adenosine diphosphate, for thromboxane, for thrombin, for serotonin, and for epinephrine, and through some less-known receptors, such as receptors for platelet activating factor, for histamine, and for high-affinity and low-affinity IgE receptors FCεRI and FCεRII.²

Thrombus formation after left atrial appendage occlusion with an Amplatzer cardiac plug device can occur months after the procedure. Nickel allergy to intracardiac devices has caused systemic allergic reactions confirmed by patch tests to nitinol, which necessitated the removal of those devices. A device syndrome resembling Kounis syndrome and consisting of chest discomfort, exertional dyspnea, palpitations, asthenia, atrial fibrillation was reported in 8 of 9 patients in a series after Amplatzer implantation. Those patients had positive patch skin test reactions to nickel.⁵

Although the rate of thrombosis complicating such devices might be low, we are still in the learning curve, and additional research is needed to prevent and treat such consequences. We recommend avoidance of metal device implantation in patients with known hypersensitivity or contraindication to any structurally related compound and to drugs these patients would need to take after implantation.

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Reply to the Editor:

My coauthors and I read with great interest the Letter to the Editor by Kounis and colleagues regarding our case report of a left atrial thrombosis of an Amplatzer patent foramen ovale (PFO) occluder (St Jude Medical, St Paul, Minn) 33 months after implantation.¹ Kounis and colleagues hypothesized that this thrombosis could be the result of the Kounis hypersensitivity-associated syndrome. This syndrome describes, among others, an allergic reaction to intracardiac metal devices (such as PFO occluders and stents) containing nickel or other metals.²

We appreciate the input from Kounis and colleagues, which might give

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important hints to our case and future device applications. Regarding our case, we explicitly asked the patient for any known allergies at the time of the operation and repeated this query after the comment from Kounis and colleagues. The patient denied any allergies; however, a skin test for sensitivity to nickel or other metals was not performed. In addition, after initial interventional Amplatzer PFO occluder implantation, the patient was without any signs of discomfort, palpitations, dyspnea, headache, pericardial effusion, or conspicuously altered laboratory values, the main symptoms of Kounis hypersensitivity-associated syndrome, for almost 33 months. The symptom that precipitated readmission to the hospital was a stroke, which was most likely due to the thrombus formation on the atrial disk of the Amplatzer device. We cannot rule out, the possibility that the Kounis hypersensitivity-associated syndrome played some role in development of this thrombus formation; however, the histologic examination of the explanted device and thrombus did not reveal any inflammatory cells. In a multicenter-study of PFO closure device explants, the rate of explants was 0.28%.³ Most of these explants were due to persistent or unknown chest pain, and half of these patients had a known nickel allergy. In addition it is shown, that in patients with known nickel allergy the rate of chest discomfort and palpitations is significantly increased after PFO device closure.⁴ None of these signs were found in our patient.

We fully agree with Kounis and colleagues that a possible nickel allergy should be ruled out before elective implantation of intracardiac metal devices. Otherwise, the patient should be made aware of the possibility of device explantation when informed consent is obtained.

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ENDOBRONCHIAL ULTRASOUND-GUIDED MEDIASTINAL LYMPH NODE NEEDLE ASPIRATION IN NON-SMALL CELL LUNG CANCER: FROM THEORY TO PRACTICE

To the Editor:

We read with pleasure the article by Lee and colleagues.¹ Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a new diagnostic technique that provides a minimally invasive option for mediastinal staging in patients with lung cancer. This technique was described by Krasnik and colleagues² in 2003 and rapidly gained the interest of the scientific community. Nonrandomized studies demonstrate that EBUS-TBNA affords excellent diagnostic performance with a sensitivity ranging from 70% to 99% and a negative predictive value up to 98%.³ Those excellent preliminary results convinced the American College of Chest Physicians to advocate EBUS-TBNA to stage the mediastinum only 4 years after the first description of the technique.

In 2006, we had the opportunity to use the first dedicated bronchoscope imported to Italy, and the potential of EBUS-TBNA was immediately obvious. The short learning curve,

high diagnostic accuracy, minimal invasiveness, and possible surgical sparing encouraged us to use EBUS-TBNA even outside of lung cancer staging.⁴

In a paradoxical way, the excellence of the preliminary results delayed the production of randomized studies, and to date only Annema and colleagues,⁵ pioneers in endobronchial ultrasound, published the randomized clinical trial, ASTER (Assessment of Surgical Staging Versus Endosonographic Ultrasound in Lung Cancer). In the aseptic world of scientific trials, the report by Lee and colleagues¹ attracts our attention for its ability to focus interest on clinical practice. The brilliant results reported by the authors demonstrate the high diagnostic value of EBUS-TBNA and the undoubtable skill of the operators. We do recommend rapid on-site evaluation of the specimen because it can decrease the rate of inadequate tests.

Reports with strong clinical characteristics, as well as randomized trials, are needed to validate EBUS-TBNA, especially for its potential capability of avoiding unnecessary surgery.

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