ponin levels, many others have reported that troponin levels are elevated during chemotherapy, a phenomenon that was correlated to the extent of the impairment of left ventricular systolic performance. Some other similar studies have provided evidence for a correlation between higher troponin levels and low left ventricular ejection fraction. Cardinale et al. (2) determined troponin I levels before, during, immediately after, and one month after chemotherapy in 703 cancer patients. The percentage of patients with persistently negative troponin I levels was 70%, that of patients with troponin elevation only in early evaluation was 21%, and that of patients with troponin elevation in both early and late evaluations was 9%. During a 3.5-year follow-up, adverse cardiac events were reported in 1%, 37%, and 84% of the subjects, respectively. These results suggest that troponin I can be used to determine the risk of cardiotoxicity both during and after chemotherapy.

Brain natriuretic peptide has a prognostic value in heart failure. Many studies scrutinizing chemotherapy-induced cardiotoxicity have provided evidence of increased BNP levels in subjects with impaired myocardial function. Sandri et al. (3) examined N-terminal proBNP levels before, at the onset of, and 72 h after chemotherapy in 52 cancer patients. They reported a strong correlation between persistent N-terminal proBNP elevation at an early period after chemotherapy and cardiac dysfunction.

There are a limited number of studies examining the role of BNP and troponins combined. In an experimental rat model where they administered intravenous 2 mg/kg doxorubicin for 8 weeks, Koh et al. (4) reported that the increase in BNP and troponin levels and the reduction in fractional shortening (FS%) were significant through 6^{th} to 12^{th} weeks, with the reduction in FS% being significantly negatively correlated to increases in BNP and troponin T levels. They also reported that the increase in troponin T level preceded that in BNP level and the decrease in FS%. Sawaya et al. (5), in a study involving 43 breast cancer patients receiving anthracycline and trastuzumab, found that troponin I and longitudinal strain were predictive of cardiotoxicity, whereas ejection fraction and N-terminal proBNP failed to predict cardiotoxicity.

In conclusion, there is some evidence that elevated troponin levels and persistent BNP elevation during chemotherapy are the risk factors for cardiotoxicity. We are of the opinion that whether an increase in troponin I levels precedes the one in BNP levels should be further tested by experimental and clinical studies.

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Late huge thrombus formation after percutaneous closure of an atrial septal defect with an Amplatzer septal occluder: Implications of Kounis syndrome

To the Editor,

Common causes of thrombus formation following implantation of cardiac devices include incorrect device placement, device size, device instability, hypersensitivity to device components, foreign body reaction, anticoagulation, and antiplatelet therapy monitoring. In the very important paper entitled "Huge thrombus formation 1 year after percutaneous closure of an atrial septal defect with an Amplatzer septal occluder" published in the Anatolian Journal of Cardiology (1), a 17-year-old boy who was diagnosed with an atria septal defect (ASD) developed a huge mobile thrombus one year after an Amplatzer septal occluder device implantation. The thrombus and device were surgically removed, and examination of the thrombus revealed the presence of peripheral blood elements and fibrin but not acute or granulomatous inflammation. Although the authors did not describe any symptomatology or electrocardiographic findings, it is presumed that the peripheral blood elements in the removed thrombus were red cells, lymphocytes, monocytes, and multinucleated leukocytes including neutrophils, basophils and eosinophils.

This case raises important questions concerning the etiology of thrombus formation.

The Amplatzer septal occluder contains nitinol, an alloy composed of 45% titanium and 55% nickel. These two metals can release metal ions while they are embedded in the atrial septal defect and are directly in touch with the blood stream. Such an-

ions can react with high- and low-affinity IgE antibody receptors, the known FCγRI, FCγTII, FCεRI, and FCεRII receptors, situated on platelet surface and trigger the thrombotic cascade (2). Implanted devices, therefore, constitute an ideal surrounding for endothelial damage and dysfunction together with hemorheologic changes and turbulence as well as platelet dysfunction, coagulation, and fibrinolytic disturbances. Metals and polymers are great sensitizers that are able to produce corresponding IgE antibodies. Nickel, chromium, and cobalt induced hypersensitivity reactions in 14%, 4%, and 9% patients in the United stated and in approximately 20%, 4%, and 7% patients, respectively, in Europe (3).

In a report of patients who were allergic to nickel, as evidenced by cutaneous patch skin tests and suffering from interatrial shunts and having full nitinol Amplatzer occluder device and the low nitinol Premere closure implanted, a Kounis syndrome-like disease was developed in eight of nine patients (4). The symptoms these patients experienced were chest discomfort, exertional dyspnea, asthenia, palpitations, worsening of migraine headaches, and mild leukocytosis between postoperative days 2 and 3. All symptoms were resolved within one week with prednisone and clopidogrel administration. Interestingly, in the same report, two patients with negative skin patch testing who had occluder system implantation had postoperative atrial fibrillation that was resolved with antiarrhythmic treatment.

Thrombus formation can occur up to 5 years after Amplatzer device implantation, but this is rare. This can be explained by the fact that hypersensitivity inflammation goes through three phases: the early phase that lasts minutes; the late phase that lasts from 2 h to 2 days; and the chronic phase that follows a continuous, persistent, and repetitive allergen exposure and lasts as long as the allergen is present.

Thrombus formation on the Amplatzer device has emphasized the need for critical attitude in decision making in percutaneous closure of patent ovale (5). We therefore believe that careful history of contraindications and hypersensitivity with monitoring of inflammatory mediators and lymphocyte transformation studies would be helpful before such device implantation.

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Author`s Reply

To the Editor,

We appreciate the authors of the letter that emphasizes the hypersensitivity inflammation after the occlusion of defects with devices that contain various metals. In our report entitled "Huge thrombus formation 1 year after percutaneous closure of an atrial septal defect with an Amplatzer septal occluder" published in the Anatolian Journal of Cardiology 2016; 16: 63-4. The significance of long-term follow-up of these patients was demonstrated, and the accurate duration and type of antiplatelet therapy, and preference of imaging technique after device implantation was considered (1).

As you mentioned, nickel allergy can be the cause of systemic reactions such as chest discomfort, palpitation, and migraine headache with or without aura in patients undergoing percutaneous atrial septal defect and patent foramen ovale closure (2). As our patient had no symptoms like chest pain, palpitation, or headache, the patient's condition was not suggestive of Kounis syndrome. Furthermore the electrocardiogram was normal. However, we do agree that hypersensitivity reactions to nickel may be more common than expected in the patients that underwent defect occlusion, particularly with devices having high nickel content.

In one study, it was reported that all patients developed Kounis syndrome within 2 and 3 days after device occlusion, and all these patients presented clinical features of this syndrome (3). Although late hypersensitivity can develop and last as long as the allergen is present, it was not clear whether this reaction could occur without any symptoms that were associated with Kounis syndrome.

On the basis of the above clinical observations, we believe that nickel allergy was not the cause of thrombus formation in our patient.

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