

# “Coral Reef”-Like Calcifications: Communities of Uncomplicated Calcified Nodules

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Acute coronary syndromes (ACS) are caused by thrombotic plaque disruption, including plaque rupture (65-70%), plaque erosion (25-30%), and calcified nodules (2-5%)<sup>1</sup>. Although calcified nodules are the least frequent cause of ACS, they occur in the heavily calcified and tortuous arteries of older individuals<sup>2</sup>. Despite this, it is unclear whether calcified nodules are a culprit of arterial thrombosis or whether they are just a bystander, which is not associated with overlying thrombosis. Here we present a unique case of “coral reef”-like aortic calcifications, characterized by communities of uncomplicated calcified nodules.

A 71-year-old Japanese woman who had undergone graft replacement for aortic arch aneurysm and right femoral artery stenting was admitted to our hospital. She was on medication for hypertension. Plasma levels of LDL cholesterol, glucose, and creatinine were 90, 99, and 0.8 mg/dl, respectively. She died of acute

transmural infarction of the small intestine. The most striking autopsy finding was a “coral-reef”-like structure in the aorta, occupying nearly half of the aortic surface, which consisted of groups of calcified grains, typically millet- to pea-sized konpeito\*<sup>1</sup>-like spheroid nodules covered by tiny bulges (Fig. 1). Some nodules were isolated, and others were fused with each other. They were grey-white and slightly shiny. The surface was seemingly smooth, and there was no superficial thrombosis. The wall of the background aorta was hard because of dense calcifications.

Histological examinations revealed “coral reef”-like calcifications, consisting of protruding clusters of calcified nodules that bulged irregularly and had a convex luminal surface through a disrupted intima with a fractured calcific plate (Fig. 2a-f). The surface was covered by a thin or extremely thin cap lined with endothelium-like cells, generally accompanied by



**Fig. 1.** “Coral reef”-like calcifications occupying nearly half of the aortic surface

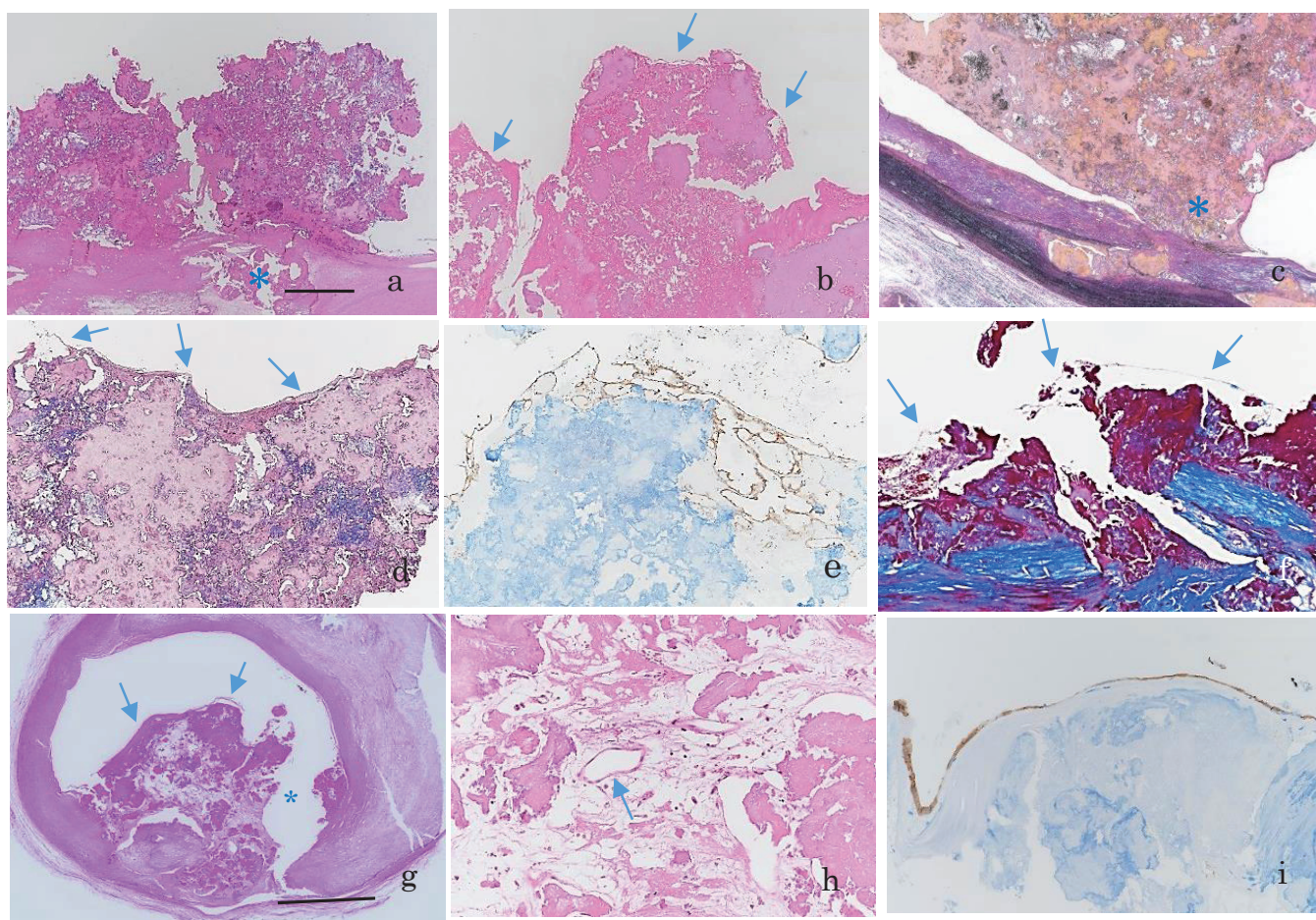
They vary in size from millimeters to reaching several centimeters (some are shown by arrows in the left) and consist of groups of calcified “konpeito”-like polypoid protrusions covered by tiny horns (right). Representative “konpeito” grains are shown by circles.

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**Fig. 2.** Histology of “coral reef”-like calcifications (a-f)

a. Routine histology showed clusters of calcified nodules protruding, irregular and convex luminal surface through a disrupted intima with a fractured calcific plate (\*). The basic architecture was crushed during the processing of the hard and fragile tissue. bar = 1 mm. b. Careful technologies disclosed very thin cap (arrows) covering the horny bulge of a nodule. c. This polypoid nodule was connected by a thin stalk (\*) with underlying calcified intima. The surface was smooth, reflecting encapsulation. Elastica van Gieson d. PTAH stain revealed fibrin meshwork (purple) in between calcified areas. Arrows indicate extremely thin cap overlying the nodule. e. CD31 positive endothelial cells lining the surface of the horny bulge and newly formed sinus-like dilated vessels. f. This small nodule, at first glance, was eruptive, but look closely, covered by an extremely thin cap (arrows) with a break due to artifact. Masson trichrome. Nodular calcification encountered in the coronary artery (g-i): g. A distinct nodular mass of calcium protruding into the lumen and encapsulated by a very thin cap (arrows) not complicated by thrombosis. Asterisk shows a crack due to artifact. bar = 1 mm. h. Instead of fibrin, loose fibrous tissue filled the space in between the calcified area. Arrow indicates neovascularization. i. CD34 immunostaining revealed endothelial cell coverage over the nodule.

small or very small amounts of fibrous tissue. The inner aspect of the nodule had multiple patchy, irregular calcified fragments. Fibrin and variable numbers of red blood cells were present within those calcified areas. Some polypoid nodules were broad-based or sessile, and others were connected by a narrowed base with underlying calcified intima. Immunostaining (CD31 and CD34, Dako Denmark) identified endothelial cells on the surface and newly formed vessels, which often exhibited sinus-like luminal dilatation. Thrombi were not evident anywhere. Apart from the aorta, there was a solitary lesion of nodular calcifica-

tion in the coronary artery. Histopathological analysis revealed an uncomplicated calcified nodule covered by endothelial cells with no residual superficial thrombus (**Fig. 2g-i**).

In 2000, Virmani *et al.* introduced the term ‘calcified nodule’<sup>2)</sup> for a rare type of coronary thrombosis not caused by plaque rupture or erosion. Subsequently, calcified nodules, identified in non-culprit coronary segments by intravascular ultrasound in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study<sup>3)</sup> were more prevalent than previously expected.

Surprisingly, these calcified nodules were benign, meaning they were unlikely to cause coronary events during a three-year follow-up study. More recently, Hao *et al.*<sup>4)</sup> and Saita *et al.*<sup>5)</sup> also reported uncomplicated calcified nodules, which are not associated with thrombosis. The present case provides further evidence to support their observations in the coronary artery. Furthermore, we found that calcified nodules are not merely alone. Still, under certain circumstances, they grow in clusters and assemble to form a unique community of “coral-reef”-like appearance, despite an undisrupted surface and absence of overlying thrombosis.

Calcified nodules might be related to intraplaque hemorrhage<sup>6)</sup>. On histology, this lesion is characterized by the protrusion of a distinct mass of nodular calcium inward toward the lumen, causing distension and dysfunction of endothelial cells permitting leakage of red blood cells and/or plasma diapedesis from circulation. It is worth noting that hard and brittle structure, i.e., calcium spicules and interspersed fibrin wrapped by the fragile, thin cap, can be broken easily (which causes artifacts) during processing for microscopic examination. Therefore, it is likely that some of the histological features or artifacts may be misinterpreted as a disrupted calcified nodule associated with fibrin deposition. So far, heavily calcified tortuous vessels have aroused little interest for pathologists, and “coral reef” calcifications have not been described in the textbooks. Non-culprit calcified nodules remain a mystery because its etiology and pathogenesis is still uncertain, and the pathophysiological significance needs further investigation.

<sup>#1</sup>The word *konpeito* comes from the Portuguese word *confeito*, which is a kind of sugar candy. *Konpeito* grains are rather small, usually 5 to 10 mm in diameter, roughly spherical, but covered with many horns.

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## Conflicts of Interest

None.

## References

- 1) Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R: Pathophysiology of atherosclerosis plaque progression. *Heart Lung Circ*, 2013; 22: 399-411
- 2) Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM: Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*, 2000; 20: 1262-1275
- 3) Xu Y, Mintz GS, Tam A, McPherson JA, Iñiguez A, Fajadet J, Fahy M, Weisz G, Bruyne BD, Serruys PW, Stone GW, Maehara A: Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: a 3-vessel intravascular ultrasound analysis from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). *Circulation*, 2012; 126: 537-545
- 4) Hao H, Fujii K, Shibuya M, Imanaka T, Kawakami R, Hatakeyama K, Asada Y, Matsuyama T, Hirota S: Different findings in a calcified nodule between histology and intravascular imaging such as intravascular ultrasound, optical coherence tomography, and coronary angiography. *JACC Cardiovasc. Interv.*, 2014; 7: 937-938
- 5) Saita T, Fujii K, Hao H, Imanaka T, Shibuya M, Fukunaga M, Miki K, Tamaru H, Horimatsu T, Nishimura M, Sumiyoshi A, Kawakami R, Naito Y, Kajimoto N, Hirota S, Matsuyama T: Histopathological validation of optical frequency domain imaging to quantify various types of coronary calcifications. *Eur Heart J Cardiovasc Imaging*, 2017; 18: 342-349
- 6) Virmani R, Burke AP, Farb A, Kolodgie FD: Pathology of the vulnerable plaque. *J Am Coll Cardiol*, 2006; 47 (8 Suppl): C13-8