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Arterial calcifications in a 96-year-old vasculopathic lady

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1. Case presentation

RS is a 96-year-old lady who presented to the emergency department from a private hospital with symptoms of decompensated heart failure. This was in the context of a recent hospital admission for lower limb cellulitis, hospital acquired pneumonia, acute kidney injury on a background of chronic kidney disease (CKD) and congestive cardiac failure. RS has an extensive history of cardiovascular risk factors, notably hypertension, dyslipidemia and type II diabetes mellitus, which had resulted in past myocardial infarctions and strokes. On clinical assessment, her decompensated heart failure was complicated by delirium. A radiograph was taken of her left wrist as RS was suspected of having a wrist injury secondary to a fall during a delirious episode. After discussion with her family and the geriatrics team, she was admitted under geriatrics for ward-based management of fluid overload and a possible superimposed infection.

Figures 1 and 2 depict extensive vascular calcifications present in RS's arteries. The common risk factors for vascular calcifications are hypertension, diabetes mellitus, dyslipidemia, age, genetics and smoking [1]. RS possesses 4 of these 6 risk factors, but complicating her risk factors is her CKD. Vascular calcifications are much more common and more severe in patients with CKD due to the abnormal mineral metabolism causing hyperphosphatemia and hypercalcaemia [1]. CKD patients are also in a state of increased oxidative stress causing vascular damage to the intimal and medial layers [1]. This increased oxidative stress can modify proteins via reactive carbonyl compounds, leading to eventual formation of advanced glycation end products which accelerate vascular calcification [1].

2. Discussion

By the seventh or eighth decade, vascular calcification is almost universal, but the degree and distribution of calcification varies widely among individuals [2]. Vascular calcifications are not as benign as initially believed by doctors; vascular wall calcifications have been associated with an increased cardiovascular risk, independent of the classical cardiovascular risk factors such as smoking, hypertension, hyperlipidaemia and diabetes mellitus [3]. The chemical composition of vascular calcifications resembles hydroxyapatite found in bone and the development of calcifications is roughly linked with the development of atherosclerosis [4]. There is some evidence suggesting that vascular calcifications are harbingers of atherosclerotic plaque instability [5]. Consequently, the severity and location of vascular calcification may be used as a surrogate biomarker to identify and risk stratify individuals destined to suffer atherosclerotic clinical symptoms [5]. The evidence for this is controversial and beyond the scope of this discussion.

Vascular calcifications, specifically arterial calcifications, can be classified into two categories: medial and intimal calcifications. Medial calcifications are independent of the development of atherosclerosis. In contrast, intimal calcifications are often involved in the atherosclerotic plaque adjacent to the medial layer of the artery and have been implicated in plaque disruption and thrombosis [5]. Medial calcifications are observed more commonly in poorly managed metabolic and electrolyte disorders [6]. Common examples would be end-stage renal disease (ESRD) and diabetes mellitus [6]. Vessels that are less likely to develop atherosclerosis are more likely to be affected by medical calcifications. Examples are abdominal visceral, thyroid

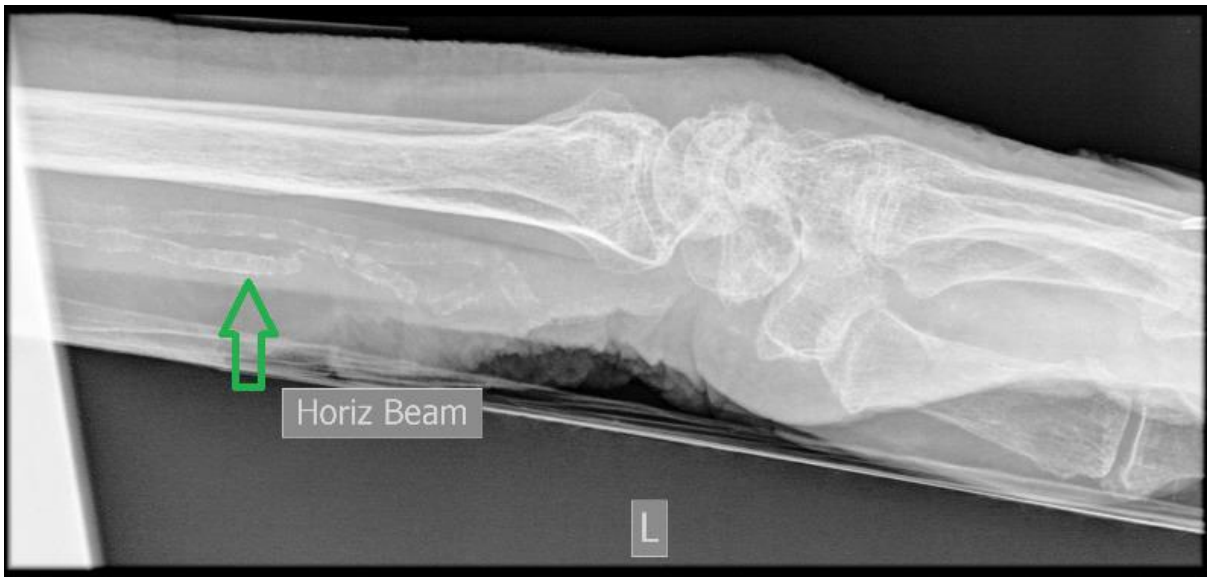

Figure 1. Lateral radiograph of left wrist. Note the extensive calcifications present in her arteries as shown by the green arrow.

and breast arteries [5]. Intimal calcifications frequently occur at sites of haemodynamic stress as these sheer forces lead to adaptive intimal thickening best described as fibromuscular proliferation [7]. Initially focal clumps of mineralised regions may develop at basal intimal regions immediately adjacent to the media. Over time these foci may undergo osseous metaplasia, and contain hematopoietic marrow, osteoblast-like cells, chondrocyte-like cells, multinucleated osteoclast-like cells. These foci also contain proteins typically associated with bone metabolism and not expressed in normal arteries [5].

Currently, controversy remains regarding whether vascular calcification is a cause or consequence of cardiovascular disease. Current evidence suggests both: a consequence as atherosclerosis induces cellular osteogenic differentiation; and a cause as vascular calcification stiffens arteries and alters plaque stability resulting in a compliance mismatch at the rigid mineral and distensible artery wall interface. Under mechanical stress (i.e turbulent flow) this interface has an increased risk of mechanical failure (e.g. plaque rupture) [7].

Given the adverse consequences of dysregulated biomineralisation, calcium-phosphate metabolism is tightly regulated, and mineralisation localised to the skeleton by endocrine and paracrine signals. Therefore any mineralisation outside the skeleton was historically viewed as a passive degenerative process [7]. Current research suggests otherwise; that vascular calcification, like osteogenesis, is a balance between activators and inhibitors. It is postulated that vascular calcifications arise from developmental programmes responsible for embryonic ossification but now modulated by inflammatory or metabolic phenomena. Chronic oxidative stress alters the inflammatory response of vascular cells, causing them to display lineage plasticity [7]. The strongest evidence for this is the presence of bone-like tissue in atherosclerotic arteries and valves. When pathologists surveyed such lesions, cells from all stages of endochondral ossification, hematopoietic cells, vascular sinusoids, marrow adipocytes, and marrow stromal cells were noted [7]. This empirical evidence suggests that mesenchymal cell plasticity has a significant active role to play in the process of vascular calcifications.

Clinically, vascular calcifications in conjunction with atherosclerosis cause a chronic progressive narrowing of the arterial lumen causing ischaemia in the downstream organs [8]. Acute coronary events or infarctions result from the biomechanical instability and subsequent rupture of the atherosclerotic plaques and their fibrous caps. Exposed collagen and other thrombogenic material then triggers primary and secondary haemostasis [8]. This phenomenon is more closely associated with intimal calcifications rather than medial calcifications. Medial calcifications promote arterial stiffness leading to increased aortic impedance and abnormal arterial pressure wave (i.e increased systolic and decreased diastolic pressures causing widened pulse pressures) [8]. Regardless of type, vascular calcifications impact left ventricular hypertrophy and cardiovascular mortality.

Vascular calcifications rarely resolve spontaneously, hence management revolves around the prevention of new calcifications and stabilisation of existing calcifications [8]. The management of intimal calcifications is largely the same as the management of atherosclerosis, namely pharmacologically management of blood lipids, blood pressure, blood glucose and platelet aggregation [2, 8], and lifestyle modifications to physical activity, diet, weight, and smok-

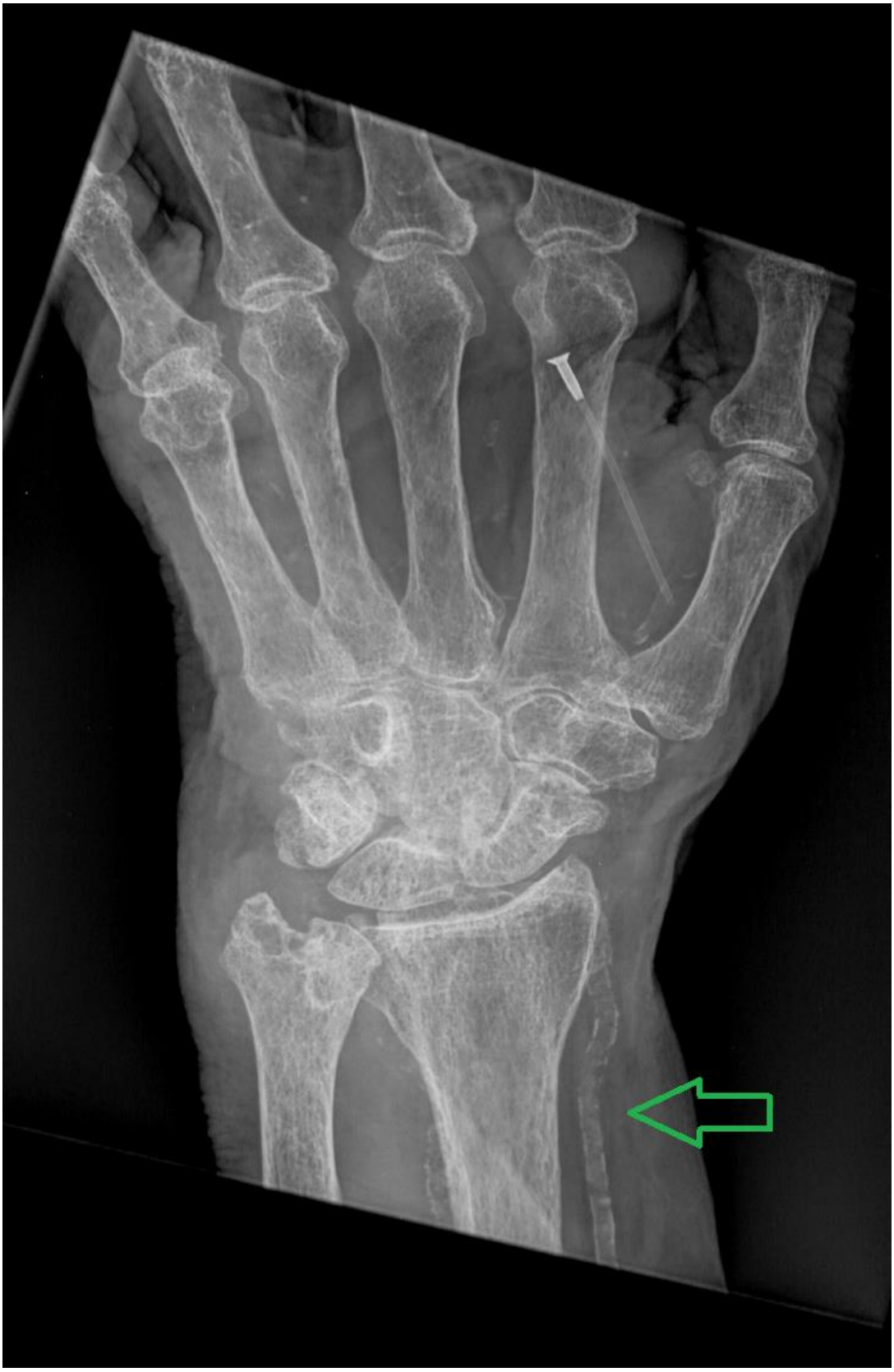

Figure 2. Anterior-posterior left wrist radiograph. Note the extensive calcifications highlighting the course of the radial artery as shown by the green arrow.

ing status. For medial calcifications, prevention of renal osteodystrophy in patients with CKD or ESRD is key [8]. A tighter control of serum calcium and phosphate levels is necessary using dietary modification, phosphate binders, calcium and vitamin D supplementation.

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