REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Heterotopic ossification of the cardiac papillary muscles: anatomical evidence, comparative pathology and mechanistic perspectives

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Abstract

Introduction: Cardiovascular calcification is common, whereas true heterotopic ossification of myocardium is rare. Papillary-muscle lesions are especially prone to terminological confusion because imaging demonstrates mineralization but cannot establish osteoid or bone. The papillary muscle is also mechanically distinctive, shortening against chordal tension at every cardiac cycle. *Aim*: To define the evidentiary criteria for papillary-muscle ossification, reconstruct its comparative and human chronology, and identify the earliest histologically documented human case. *Methods*: A narrative historical review combined structured *PubMed* searching, citation-chain tracing and examination of primary reports. Priority was given to reports with explicit papillary-muscle localization and histological evidence of bone, or an unequivocal osteogenic sequence. *Results*: Cardiac chondro-osseous metaplasia was described in rats in 1946. Cartilaginous and osseous metaplasia was localized to the rat papillary muscle in 1976 and reproduced experimentally in the papillary muscle and subendocardium after coronary ligation in 1995. Human papillary-muscle reports before 2011 documented fibrosis or calcification without bone. A 2011 autopsy report then described focal osseous metaplasia, diffuse osteoid, an osseous plate and primitive trabecular bone within extensively calcified posteromedial papillary muscles. Comparative studies show that *os cordis*, atrial osteocartilaginous metaplasia and papillary-muscle ossification are anatomically distinct entities. *Conclusions*: That 2011 report appears to provide the earliest identifiable published histopathological demonstration of trabecular bone within a human cardiac papillary muscle; the animal precedent is 35 years earlier. Whether human papillary-muscle bone follows a transient endochondral phase, direct fibroblast-associated osteogenesis, or both remains unresolved.

Keywords: papillary muscle, heterotopic ossification, cardiac calcification, myocardial infarction, chondrogenesis, papillary-muscle development.

Introduction

The papillary muscles are specialized muscular columns of the ventricular myocardium that transmit force through the *chordae tendineae* to the atrioventricular valve leaflets. Ischemia, rupture, fibrosis, calcification or impaired contractility can therefore compromise valve competence. The posteromedial papillary muscle is particularly vulnerable because its arterial supply is often less redundant than that of the anterolateral group, although its feeding vessels may arise from either coronary circulation [1, 2]. Anatomically, each papillary muscle is a discrete myocardial unit with its own base of ventricular attachment, its own body and apex, and its own terminal vascular territory, and it is on that territorial arrangement, rather than on any property of the myocardium at large, that its selective vulnerability depends. In ink-injected human hearts, each left papillary muscle is supplied by one or two main arteries that penetrate it longitudinally and branch from segmental centers, the posteromedial muscle being supplied from the right coronary system in most hearts; intramuscular sources overlap segmentally and are reinforced by capillary extensions of the mural networks [3].

Developmentally, the mitral papillary muscles are derivatives of the trabecular myocardium. In human embryos, a horseshoe-shaped trabecular ridge runs from the anterior wall through the apex to the posterior wall of the left ventricle; its anterior and posterior parts delaminate from the ventricular wall and become the anterolateral and posteromedial papillary muscles, while the atrioventricular cushion tissue attached to them remodels into leaflets and chordae [4]. Each papillary muscle is therefore a trabecular, endocardium-covered structure that remains in continuity with cushion-derived connective tissue of the chordae. This developmental origin is worth keeping in view when the metaplastic lesions discussed below are found in the papillary muscle, the chordae and the subendocardium.

Calcium deposition and bone formation must be separated. Dystrophic myocardial calcification occurs in injured or necrotic tissue and may consist of intracellular and extracellular calcium phosphate mineral associated with damaged organelles and membranes [5, 6]. Ossification, by contrast, requires an organized osteogenic process that produces osteoid and bone matrix, sometimes through a cartilage intermediate and sometimes directly within connective tissue. Thus, radiopacity, echogenicity, computed tomography (CT) attenuation or uptake of a bone-seeking tracer establishes mineralization, not bone. Soft-tissue mineralization is conventionally divided into dystrophic, metastatic, idiopathic and iatrogenic categories [7]. In a series of 1177 patients with surgically excised cardiac valves, metaplastic bone and/or cartilage was found in 128 (10.9%), the 128 cases of the article's title; bone was present in 103 (8.8%; bone alone in 84, bone with cartilage in 19), was lamellar with

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predominantly fatty marrow, and every valve with metaplasia was calcified [8]: in cardiac tissue, bone typically develops on, rather than instead of, a calcified substrate.

For historical priority, the decisive evidence is morphological: osteoid or mineralized bone matrix, osteocytes in lacunae, osteoblast or osteoclast participation, trabeculae, marrow-like spaces or a recognizable cartilage-to-bone transition. This review applies that evidentiary threshold to a small and fragmented literature, while keeping physiological or species-associated cardiac skeletal bone, atrial osteocartilaginous metaplasia and papillary-muscle heterotopic ossification anatomically separate.

The relevance of papillary-muscle ossification extends beyond historical priority. Papillary muscles function under repetitive tensile loading, and infarction alters both their mechanical environment and extracellular matrix. Experimental cardiac chondro-osseous metaplasia has repeatedly been associated with altered mechanical conditions; whether mechanotransduction contributes to bone formation in the human papillary muscle has not been examined. This raises the question of why heterotopic bone forms in this particular ventricular structure.

Accordingly, this review examines the morphological distinction between calcification and ossification, the comparative anatomical record, and the cellular mechanisms that may account for bone formation at this site (Figure 1, A and B).

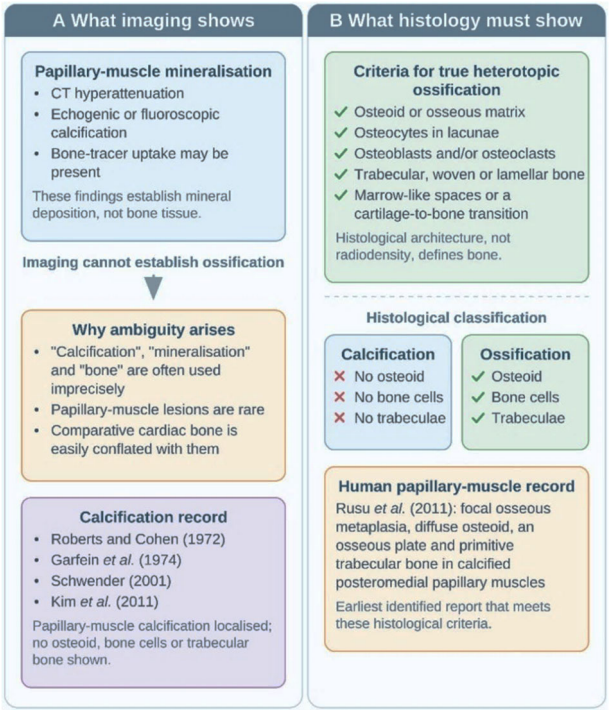

Figure 1 – ***Distinguishing papillary-muscle calcification from true heterotopic ossification: (A) Imaging-defined papillary-muscle mineralization establishes calcification but does not prove bone; (B) True heterotopic ossification requires histological evidence such as osteoid, osteocytes in lacunae, osteoblasts and/or osteoclasts, trabecular or woven bone and, in some lesions, a cartilage-to-bone transition. CT: Computed tomography.***

Methods

This work is a narrative historical review rather than a formal systematic review. *PubMed*/*MEDLINE* was searched from inception; the final search was run on 22 September 2026. The principal search strings were: (*i*) ("papillary muscles"[MeSH] OR "papillary muscle"[tiab]) AND (ossification OR osseous OR bone OR osteoid OR cartilaginous OR chondroid OR metaplasia OR calcification OR calcified); (*ii*) (heart[ti] OR myocardium[ti] OR myocardial[ti] OR cardiac[ti]) AND (ossification[ti] OR "bone formation"[ti] OR "osseous metaplasia"[ti]); and (*iii*) "*os cordis*" OR "*cartilago cordis*" OR (cardiac AND chondrogenesis). Mechanistic searches combined sex determining region Y (SRY)-box transcription factor 9 (Sox9), RUNX family transcription factor 2 (Runx2), Adam19/Alk2, Piezo1, chondrocyte transdifferentiation and lineage tracing with heart or myocardium. Consensus (*Semantic Scholar*, *OpenAlex*) and Asta (Allen Institute for AI) served as supplementary search engines. The case set of a recent systematic review of extensive myocardial calcification, which covered *PubMed*, *OVID–MEDLINE* and the *Cochrane Library* to June 2023 but did not distinguish ossification from calcification, was used as an external cross-check [9]. Because reports published before about 1950 are inconsistently indexed, older material was located by backward and forward citation tracing from retrieved primary reports and reviews, in particular [2, 5, 6] and the human case reports of 1937–1949 [10–12], and by retrieval from publisher archives. Every report that potentially described cardiac bone or cartilage was read in full. Earlier reports of cardiac "ossification" (1761–1912), known only through citation in [10, 12], either lacked histological examination, concerned the atrioventricular grooves or the atrial wall, or could not be retrieved in full; none described a papillary-muscle lesion. A later report of calcification with ossification of a left-ventricular infarct (Borman, 1943), cited in [12], could not be retrieved in full. The literature set and bibliography were last re-checked in October 2026.

A report was considered to establish papillary-muscle ossification only when the anatomical location was explicit, and histology demonstrated bone or an unequivocal osteogenic sequence. Imaging-only descriptions were retained as calcification records but were not counted as evidence of ossification. Human cardiac bone outside the papillary muscles and physiological or species-associated cardiac skeletal bone were classified separately. Priority-defining claims were checked against original articles when obtainable; conference abstracts and secondary summaries were not used to establish priority. Bibliographic details were re-checked against *PubMed* or publisher metadata, and final-issue publication years were used when online-first and issue years differed. Evidence was organized chronologically and interpreted by anatomical compartment and evidential level; mechanistic studies were used to assess biological plausibility, not to redefine historical lesions retrospectively.

Archival micrographs

To illustrate the histological threshold applied in this review, previously unpublished micrographs of the Hematoxylin–Eosin (HE)-stained sections of the 2011 autopsy case [13] were retrieved from the author's archive. They are the original color camera files (Zeiss AxioCam, captured in 2010), processed only by uniform scaling, panel assembly and lettering; no color, contrast or content adjustment was applied, and no generative or AI-based tool

was used to create or alter the images. None of the six fields was reproduced in the 2011 report, although some depict lesions that were shown there in adjacent fields or at a different magnification. The archival files carry no scale bars. Objective magnifications were reconstructed from the archive itself, in which overlapping fields of the same lesions recur at exactly twofold steps (feature-based image registration), and scale bars were calibrated on the diameter of intravascular erythrocytes (taken as 7 μm); both are given in the legend.

Anatomical and histopathological evidence

Evidence hierarchy

Literature can be separated into three evidentiary levels. Imaging or gross radiopacity establishes mineralization. Routine histology can establish calcification and tissue injury. True heterotopic ossification requires bone architecture or a recognizable osteogenic sequence. The papillary-muscle calcification record comprises imaging-defined cases [14–17], whereas the ossification record comprises reports with histological bone or an unequivocal osteogenic sequence [13, 18, 19]. These levels are summarized in Figure 1 (A and B), and the primary reports are arranged chronologically, with their level of evidence and papillary-muscle localization, in Table 1 ("Chronological synthesis" subsection).

Animal papillary-muscle ossification

The animal record predates the human report by decades. Farris *et al.* (1946) described cardiac chondro-osseous metaplasia in rats, usually near the left-ventricular apex, but the spicules were attached loosely to the endocardium, some lying free in the ventricular lumen, and their relation to the papillary muscles was not stated [20]. Sharma (1976) provided the first explicit papillary-muscle localization: a rat with severe cardiomyopathy showed cartilaginous and osseous metaplasia in papillary muscle, *chordae tendineae*, subendocardium and left-ventricular myocardium, with bony spicules and primitive hematopoietic tissue [19]. The animal was a 370-day-old male Charles River-CD rat in which fibrous tissue differentiated into hyaline cartilage and bone, and the figure caption explicitly identifies cartilaginous and osseous metaplasia of the papillary muscle with primitive hematopoietic cells [19]. This is an unequivocal mammalian papillary-muscle precedent, 35 years before the human case.

Asanuma *et al.* (1995) converted that anatomical observation into an experimentally reproducible post-infarction phenomenon [18]. Four weeks after coronary ligation, cartilaginous and osseous metaplasia was present in all 15 infarcted spontaneously hypertensive rats and in 13 of 15 infarcted Wistar–Kyoto rats, but in none of the non-infarcted controls [18]. The lesions occupied infarction zones of the papillary muscle and subendocardium near the apex [18]. They included cartilage, osseous matrix with osteocytes, osteoblasts and osteoclasts, with sections showing transition from cartilage to bone [18].

Ribeiro *et al.* (2006) later showed that post-infarction cardiac ossification in rats is reproducible rather than anecdotal: mature lesions contained cartilage, bone and marrow-like structures in a collagen-rich scar, with hydroxyapatite demonstrated in the mineral phase; the lesions were not assigned to a papillary muscle [21]. Manole *et al.* (2019) subsequently documented post-infarction chondroid/osseous metaplasia in the papillary-muscle region with ultrastructural analysis, explicitly citing the Asanuma model as precedent [22]. In that study, however, only two of 69 infarcted rats developed such lesions [22], in contrast with the near-constant incidence reported in hypertensive and normotensive strains by Asanuma *et al.* (1995) [18]; strain, model and timing therefore appear to modulate the response.

A separate, iatrogenic route to cardiac bone must be kept apart from this record. After myocardial infarction in mice, encapsulated structures containing calcification and/or ossification developed in 22 of 43 hearts injected with mesenchymal stromal cells and in 6 of 46 hearts injected with unfractionated bone marrow, but in none after purified hematopoietic progenitors, fibroblasts, vehicle or cytokine-induced marrow mobilization [23]. Infarcted myocardium can therefore host bone formed by an introduced osteogenic-competent cell population, a mechanism distinct from spontaneous papillary-muscle ossification but relevant to any future human case examined after cell therapy.

Human papillary-muscle record and the 2011 milestone

Human cardiac ossification was recognized long before 2011. Cohen & Levine (1937) reported myocardial calcification with bone formation; Edelstein (1946) and Finestone & Geschickter (1949) provided further histological descriptions [10–12]. These reports establish human myocardial bone formation but differ in how far they permit the papillary muscles to be assessed. Finestone & Geschickter (1949) located the bone in a mass in the lateral wall of the right ventricle and explicitly described the papillary muscles as unremarkable [12]. Cohen & Levine (1937) demonstrated osseous trabeculae with marrow spaces in the wall of a post-infarction left-ventricular aneurysm occupying the distal three-fifths of the ventricle but did not describe the papillary muscles [10]. Edelstein (1946) found ossification in many fields of a diffusely calcified myocardium involving both ventricles of an 11-year-old boy, without specifying the sampled sites [11]. Papillary-muscle involvement is therefore excluded in one report and cannot be established from the other two; none localizes constituted bone to a papillary muscle.

The human papillary-muscle literature followed a different path. Roberts & Cohen (1972) documented marked fibrosis, atrophy and calcification of an anterolateral papillary muscle in a child with anomalous origin of the left coronary artery [2]. Garfein *et al.* (1974), Schwender (2001) and Kim *et al.* (2011) demonstrated papillary-muscle calcification by radiography, fluoroscopy, echocardiography or CT, but none documented osteoid or trabecular bone [15–17].

Rusu *et al.* (2011) described extensively calcified posteromedial papillary muscles in a 73-year-old man with previous myocardial infarction, type 2 diabetes, hypertension, heart failure and diabetic nephropathy. Histology showed a preserved peripheral muscular sleeve surrounding a fibrohyaline core containing focal osseous metaplasia, diffuse osteoid/osseous matrix, an osseous plate, rare osteoclasts and focal primitive trabecular bone. Other areas showed calcium embedding of former muscle fibers with intercalated discs still recognizable. The lesion therefore contained both degenerative mineralization and organized osteogenesis [13]. The patient died of septic shock from a perforated duodenal ulcer; autopsy also documented concentric left-ventricular

hypertrophy, old anterolateral and inferior infarcts, systemic arteriosclerosis and chronic pyelonephritis. The authors termed the calcium embedding of preserved fibers "mummification" and proposed a multifactorial sequence in which ischemic necrosis provided a local calcified substrate, the systemic metabolic milieu favored mineral deposition, and local mesenchymal or fibroblast-lineage cells acquired osteoblast-like phenotypes [13]. That cellular mechanism was an inference in 2011; later lineage-tracing work in murine hearts ("Fibroblast-associated osteogenic route" subsection) showed that cardiac fibroblasts can adopt osteogenic phenotypes but has not established the origin of the bone in this lesion.

Additional micrographs of the same archived HE sections (Figure 2, A–F), captured in 2010 but not included in the 2011 report [13], illustrate, at low to intermediate magnification, the architecture of the lesions present within a single fibrohyaline core: fusiform and plate-like eosinophilic formations aligned with the axis of the muscle, a nodular focus, lacunar matrix with intertrabecular spaces (Figure 2, D and E) and, in contrast, brittle dystrophic mineral deposits without bone architecture (Figure 2F). At these magnifications cells cannot be resolved within the lacunae; the cellular criteria rest on the original sections, on which the 2011 report documented osteoid and osteoclasts and found the osteocyte lacunae of the constituted bone largely empty, as expected in necrotic bone [13]. Calcification and ossification therefore coexist within the same papillary muscle, and only the latter meets the criteria of "Evidence hierarchy" subsection.

Subsequent reports have not established an earlier human papillary-muscle case. Ávila-Vanzzini *et al.* (2014) documented idiopathic left-ventricular myocardial osseous metaplasia, with bony spicules and spongy trabecular bone containing marrow; papillary-muscle localization of the histologically proven bone was not established [24]. Nollet *et al.* (2025) reported extensive left-ventricular papillary-muscle calcification in adenosine triphosphate (ATP)-binding cassette subfamily C member 6 (*ABCC6*)-related *pseudoxanthoma elasticum* by multimodality imaging, but without histological evidence of bone [14]. On the criteria applied here, the 2011 report remains the earliest identified published histopathological demonstration of trabecular bone within a human papillary muscle [13]. Conversely, the statement in the 2011 report that bone had not previously been demonstrated in a papillary muscle is not sustainable across species, given the rat observations of Sharma (1976) and Asanuma *et al.* (1995); the priority holds for the human papillary muscle only [13, 18, 19].

Chronological synthesis

Table 1 arranges the primary reports discussed above chronologically and records, for each entry, the species, the anatomical compartment involved, the level of evidence attained (imaging, histology showing calcification, or histology showing bone or cartilage) and whether papillary-muscle involvement is explicit, excluded or not determinable from the report, according to the hierarchy of "Evidence hierarchy" subsection.

Comparative cardiac bone and cartilage

Bone in the heart is not a single anatomical entity. Gopalakrishnan *et al.* (2007) found mature lamellar bone with occasional endochondral ossification in the right atrial myocardium of clinically normal adult sheep; the surrounding myocardium lacked degenerative change [25]. Moittié *et al.* (2020) identified *os cordis* or *cartilago cordis* within the right fibrous trigone of chimpanzees, particularly in hearts with marked myocardial fibrosis [26]. Trainini *et al.* (2021) described a rigid cardiac fulcrum beneath the right trigone: bovine specimens contained trabecular osteochondral tissue, whereas adult human specimens were tendon-like rather than osseous [27]. These entities occupy the cardiac skeleton or atrial wall and should not be conflated with post-ischemic papillary-muscle ossification. The ovine foci were palpable in 3.49% of 172 animals [25]; among 16 chimpanzee hearts examined by micro-CT and histology, two trigonal structures contained trabecular bone, one hyaline cartilage and one mineralized fibrocartilaginous metaplasia with endochondral ossification [26]; and in the fulcrum series a 10-year-old human specimen showed a chondroid central zone and a fetal specimen prechondroid tissue [27].

Cardiac chondrogenesis is nevertheless biologically relevant. López *et al.* (2003) and Durán *et al.* (2004) documented development of cartilage in the cardiac skeleton of the Spanish terrapin and Syrian hamster, respectively [28, 29]. In mammals, Arai *et al.* (2019) showed that cardiac neural-crest chondrogenesis is actively restrained by Adam19-dependent attenuation of Alk2/bone morphogenetic protein (BMP)–Sox9 signaling; disruption of this restraint produced ectopic cardiac cartilage [30]. Human diseased hearts also show chondroid/osseous metaplasia outside the papillary muscles, including the central fibrous body [31] and diseased valves [32]. These observations establish latent chondrogenic competence in cardiac tissues without implying a shared developmental origin for all lesions.

The developmental routes to cardiac cartilage differ. In the terrapin, a mesenchymal condensation along the aorticopulmonary septum and the incipient *pars fibrosa* began producing type II collagen at stage 23 and became hyaline cartilage without later replacement by bone [29]. In 472 Syrian hamster hearts, cartilage appeared in the central fibrous body in 25%, mostly between postnatal days 40 and 80 and without a conspicuous prechondrogenic condensation and was calcified in 5.8% of the animals examined radiographically [28]. The cellular source is not uniform either: besides the cardiac neural crest, proepicardial progenitor cells can form cardiac cartilage *in vivo* and *in vitro* [33]. Several cardiac progenitor populations therefore possess chondrogenic potential, although none has been identified as the source of post-infarction papillary-muscle metaplasia.

Mechanical loading recurs as an explanation across these settings. Cartilaginous foci of the terrapin and hamster cardiac skeleton were interpreted as structures resisting cyclical tension [28, 29], and altered chamber or ventricular mechanics were proposed as contributors to chondro-osseous metaplasia in the adolescent central fibrous body and in the infarcted rat papillary muscle [22, 31]. In a series of 1094 native valves, chondromatous metaplasia was found in 46, became more frequent with thickening, calcification and stenosis, and was more often accompanied by osseous metaplasia when cartilage was present [32]. The papillary muscle is thus a plausible mechanically permissive site, although direct mechanotransduction data from cardiac lesions are lacking.

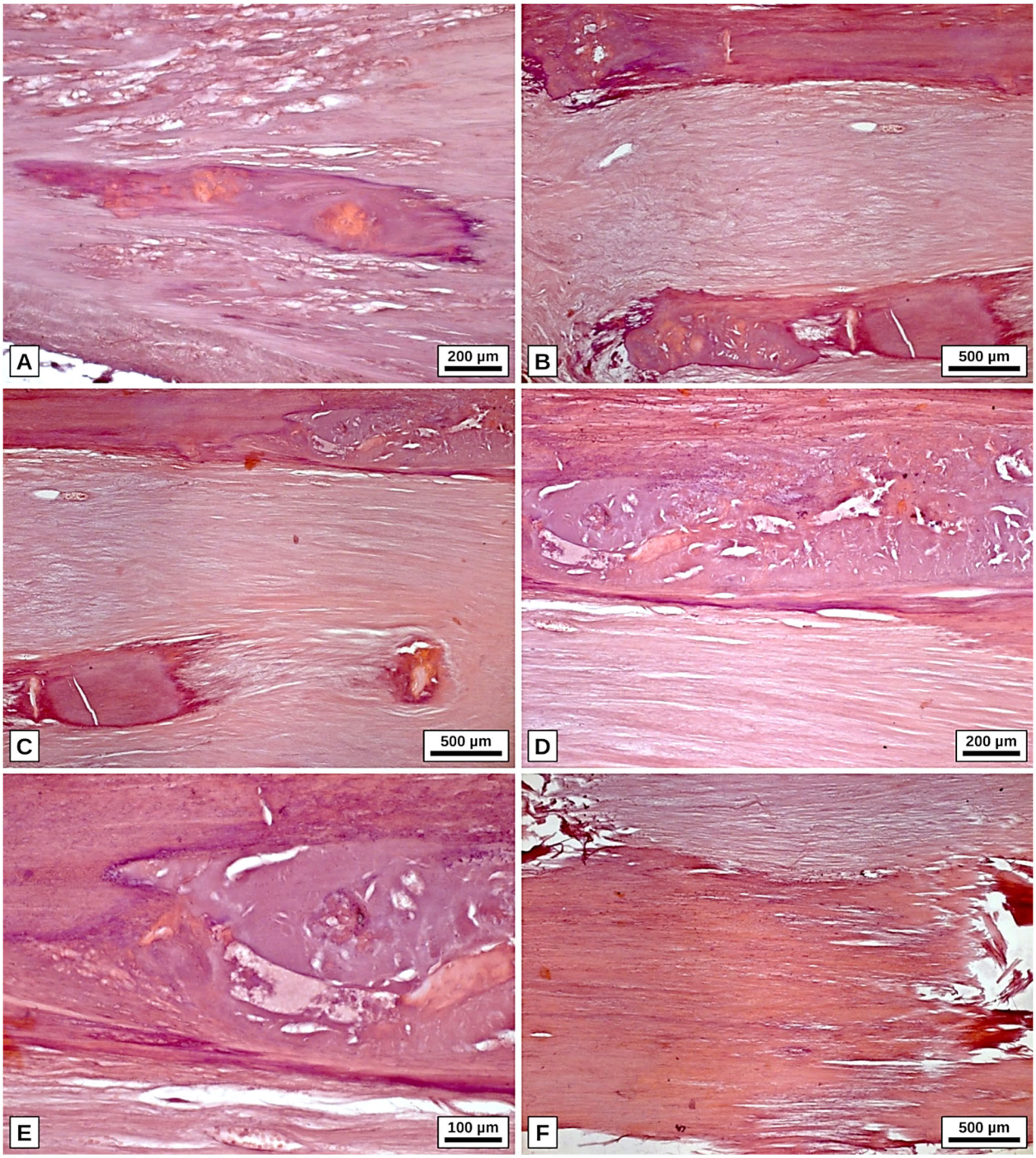

Figure 2 – ***Previously unpublished micrographs of the posteromedial papillary muscles of the 2011 autopsy case (Hematoxylin–Eosin staining; original camera files, no color or contrast adjustment). For each panel, the features directly visible at the magnification shown are described first; interpretations that rest on examination of the original sections at higher magnification, or on the 2011 report [13], are stated separately. (A) Visible: fusiform focus within the fibrohyaline core, with basophilic margins and eosinophilic–orange central foci. Interpretation: focus of osseous metaplasia, as described in the 2011 report. (B) Visible: two elongated eosinophilic formations aligned with the long axis of the core; the lower one contains small lacuna-like spaces and is crossed by a transverse cleft. Interpretation: osseous plates. (C) Visible: end of a plate-like formation (left) and a separate nodule with a central cleft (right), both surrounded by concentrically arranged collagen fibers. Interpretation: osseous plate and nodular focus of ossification. (D) Visible: plate of matrix with numerous lacunae and irregular intertrabecular spaces, sharply demarcated from the adjacent fibrohyaline tissue; this panel shows trabecular architecture most directly. (E) Visible: lacunar matrix with intertrabecular spaces containing loose material, bordered by an eosinophilic acellular deposit. Interpretation: primitive trabecular bone. (F) Visible: brittle, fragmented mineral deposit at the edge of the homogeneous fibrohyaline core (right), without lacunae or trabecular architecture – dystrophic calcification, for comparison. At these magnifications, cells cannot be resolved within the lacunae, and osteoid seams and osteoblastic rims are not identifiable; on the original sections, the 2011 report documented osteoid and osteoclasts and found the osteocyte lacunae of the constituted bone largely empty [13]. Original objective magnification ×5 (B, C and F), ×10 (A and D) and ×20 (E); Scale bars: 500 µm (B, C and F), 200 µm (A and D) and 100 µm (E).***

Table 1 – ***Chronology relevant to papillary-muscle calcification and ossification, with level of evidence and papillary-muscle localization***

Year	Species	Anatomical site	Level of evidence	Papillary-muscle localization	Key finding
1937	Human	LV, post-infarction aneurysm wall	Histology – bone	Not determinable	Cohen & Levine: osseous trabeculae with marrow spaces in the calcified aneurysm wall; papillary muscles not described [10].
1946	Rat	LV endocardial surface, at or near the apex	Histology – cartilage and bone	Not determinable	Farris *et al.*: ossifying cartilage with marrow-like cavities; relation to the papillary muscles not stated [20].
1946	Human	LV and RV, diffuse	Histology – bone	Not determinable	Edelstein: massive myocardial calcification with ossification in an 11-year-old boy; sampled sites not specified [11].
1949	Human	RV lateral wall	Histology – bone	Excluded	Finestone & Geschickter: calcified mass with bone spicules and myeloid cells; papillary muscles unremarkable [12].
1972	Human	Anterolateral papillary muscle	Histology – calcification	Explicit	Roberts & Cohen: fibrosis and calcification; no bone [2].
1974	Human	Papillary muscle	Imaging	Explicit	Garfein *et al.*: cineradiographic calcification; no tissue proof [15].
1976	Rat	Papillary muscle, chordae, subendocardium	Histology – cartilage and bone	Explicit	Sharma: cartilaginous and osseous metaplasia with primitive marrow [19].
1995	Rat (SHR/WKY)	Infarcted papillary muscle/subendocardium	Histology – cartilage and bone	Explicit	Asanuma *et al.*: cartilage and bone after coronary ligation; absent in controls [18].
2001	Human	Posteromedial papillary muscle	Imaging	Explicit	Schwender: extensive calcification by fluoroscopy/echocardiography [17].
2006	Rat	Post-infarction LV scar	Histology – cartilage and bone	Not determinable	Ribeiro *et al.*: cartilage, bone and marrow-like tissue; hydroxyapatite confirmed [21].
2011	Human	Anterolateral papillary muscle	Imaging	Explicit	Kim *et al.*: extensive calcification by echocardiography/MDCT; no histological bone [16].
2011	Human	Posteromedial papillary muscles	Histology – bone	Explicit	Rusu *et al.*: osseous metaplasia, diffuse osteoid, osseous plate and primitive trabecular bone [13].
2014	Human	LV myocardium	Histology – bone	Not determinable	Ávila-Vanzzini *et al.*: bony spicules and spongy trabeculae with marrow in LV myocardium [24].
2019	Rat	Papillary muscles after MI	Histology – cartilage and bone	Explicit	Manole *et al.*: post-infarction chondroid/osseous metaplasia with ultrastructural analysis [22].
2025	Human	LV papillary muscles	Imaging	Explicit	Nollet *et al.*: *ABCC6*-related calcification by multimodality imaging; no histological bone [14].

ABCC6: Adenosine triphosphate (ATP)-binding cassette subfamily C member 6; LV: Left ventricle; MDCT: Multidetector computed tomography; MI: Myocardial infarction; RV: Right ventricle; SHR: Spontaneously hypertensive rat; WKY: Wistar–Kyoto.

Mechanistic interpretation

Three levels of evidence are distinguished below: observations in the human papillary-muscle lesion, experimental findings in cardiac tissue, and extrapolations from skeletal research. Only the first describes the human lesion; the other two generate hypotheses.

Endochondral route

Cardiac experimental evidence

In the rat, papillary-muscle and post-infarction lesions frequently contain cartilage together with bone: Sharma (1976) and Asanuma *et al.* (1995) explicitly described cartilage-to-bone transitions, and Ribeiro *et al.* (2006) found cartilage, bone and marrow-like tissue in infarct scar [18, 19, 21]. Experimental disruption of Adam19-dependent attenuation of BMP–Sox9 signaling produces ectopic cardiac cartilage [30], showing that cardiac cells possess latent chondrogenic competence.

Skeletal extrapolation

In endochondral bone, lineage tracing shows that hypertrophic chondrocytes survive the chondro-osseous transition and become osteoblasts and osteocytes, accounting for about 60% of mature osteoblasts in one murine model [34, 35]. The switch requires physiological downregulation of Sox9, the persistent expression of which suppresses transdifferentiation [36], and in fracture repair it depends on Piezo1-mediated mechanotransduction acting on chondrocyte mitochondrial function [37]. These data suggest how an infarcted papillary muscle under cyclical tension could drive a chondrogenic programme toward bone, but no cardiac study has lineage-traced chondrocytes, and no cartilage intermediate was documented in the human lesion [13].

Fibroblast-associated osteogenic route

Human observation

In the 2011 case, osteoid and primitive trabecular bone lay within a fibrohyaline, already calcified core, without a documented cartilage intermediate, in a patient with previous infarction, diabetes, diabetic nephropathy, hypertension and heart failure [13].

Cardiac experimental evidence

In injured murine hearts, resident cardiac fibroblasts acquire osteoblast-like markers and contribute directly to hydroxyapatite deposition through induction of the ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)–pyrophosphate–phosphate axis, and susceptibility to mineralization is markedly strain-dependent [38]. These findings demonstrate fibroblast-driven mineralization, not fibroblast-derived trabecular bone, and therefore do not establish the cellular origin of the bone in the 2011 lesion.

Extrapolation

Bone formed within a stationary connective scaffold

resembles static osteogenesis, proposed together with the dynamic osteogenesis that follows it as a common denominator of pathological calcification and heterotopic ossification [39]; and in chronic kidney disease, cardiovascular calcification is an active, regulated process resembling osteogenesis [40]. Both are plausible contributors to the 2011 lesion but remain untested in it.

Current human evidence cannot distinguish between the two routes: a late-stage autopsy specimen may show bone after a transient cartilage phase has been remodeled, while a heavily calcified fibrous scaffold may support more direct osteogenesis. The 2011 patient combined previous infarction, diabetes, nephropathy, hypertension and heart failure, which supports a multiple-hit model rather than a distinct entity of "diabetic papillary-muscle ossification".

Clinical and imaging implications

Papillary-muscle mineralization is clinically relevant because the structure must shorten and maintain chordal tension during systole. Extensive calcification can alter compliance and contractile behavior, particularly when posteromedial and associated with inferior infarction or mitral regurgitation [17]. The anatomical site should therefore be reported precisely on CT and echocardiography. Mineralized lesions of the mitral apparatus can also mimic tumors: caseous calcification of the mitral annulus has been mistaken for a papillary fibroelastoma on echocardiography and cardiac magnetic resonance imaging [41].

Imaging cannot determine whether a calcified papillary muscle contains bone. Bone-seeking tracer uptake is likewise non-specific: Lucas *et al.* (2026) described intense technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) myocardial uptake in Fabry cardiomyopathy without amyloid, illustrating that affinity for a bone tracer is not equivalent to histological ossification [42]. Conversely, bone-avid tracers are used diagnostically in transthyretin cardiac amyloidosis because they accumulate in amyloid-infiltrated myocardium, not in bone [43]. For future clinicopathological studies, the most informative protocol would combine anatomical imaging with decalcified histology, calcium-specific stains and, where tissue permits, micro-CT and immunohistochemistry for osteogenic and chondrogenic markers. Osteopontin and osteoprotegerin, already assessed immunohistochemically in calcified carotid atherosclerotic plaques [44], would be suitable additions to such a panel.

Limitations and future directions

Historical priority work is constrained by incomplete indexing and variable terminology, especially before *PubMed*. The phrase "earliest identifiable" is therefore preferable to "first ever". The human priority rests on a single autopsy report, whereas most mechanistic evidence is murine and concerns ventricular injury zones rather than papillary muscles. Comparative *os cordis* and atrial studies involve different anatomical compartments and should be interpreted as evidence of cardiac skeletogenic competence, not as direct analogues of papillary-muscle disease.

Under-recognition may explain part of the rarity of human reports. A hard papillary muscle may be recorded grossly as calcified without decalcified histological sampling, heavily mineralized tissue is technically difficult to section, and imaging terminology naturally favors "calcification". Calcium-specific stains confirm mineral deposition, but the diagnosis of bone still depends on architecture [7], and a transient cartilage phase may already have been remodeled in a late-stage lesion.

Resolving this question will require systematic examination, after decalcification, of macroscopically or radiologically calcified human papillary muscles. Sampling should document precise papillary-muscle anatomy and previous infarct territory, distinguish calcification from osteoid and mature bone, and test for residual cartilage or osteogenic cell phenotypes. Such studies could determine whether human papillary-muscle ossification is genuinely exceptional or simply under-recognized.

Conclusions

Cardiac chondro-osseous metaplasia was documented in rats by 1946; Sharma (1976) explicitly localized cartilaginous and osseous metaplasia to a rat papillary muscle; and Asanuma *et al.* (1995) established a controlled post-infarction papillary-muscle/subendocardial model [18–20]. Human papillary-muscle reports before 2011 demonstrated fibrosis or calcification but not organized bone. Rusu *et al.* (2011) then documented focal osseous metaplasia, diffuse osteoid, an osseous plate and primitive trabecular bone within extensively calcified human posteromedial papillary muscles [13].

In the presently identifiable literature, that report is the earliest report that meets the histological threshold for bone within a human papillary muscle. Its significance is best understood anatomically rather than as a broad claim about "bone in the heart": *os cordis*, atrial osteocartilaginous metaplasia, post-infarction scar ossification and papillary-muscle bone are distinct entities. Experimental cardiac and skeletal evidence makes both cartilage-mediated endochondral ossification and fibroblast-associated osteogenesis plausible hypotheses, but neither lineage has yet been demonstrated directly in human papillary-muscle bone.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

This review includes previously unpublished micrographs of archival Hematoxylin–Eosin-stained sections from a single autopsy case reported in 2011 (Figure 2). The tissue was obtained at a medico-legal autopsy; no new tissue was sampled for this work, and the images contain no information that could identify the deceased; therefore, informed consent from the patient or the next of kin was not required.

Declaration of competing interests

The author declares the following competing interests. The author is a co-author of Rusu *et al.* (2011), the report whose historical priority is evaluated in this review and therefore has a direct interest in the assessment of that publication. The author additionally reports an editorial relationship with *Annals of Anatomy* and serves as an Editor of the *Romanian Journal of Morphology and Embryology*.

CRediT authorship contribution statement

Mugurel Constantin Rusu: conceptualization, methodology, investigation, data curation, formal analysis, visualization, writing – original draft, writing – review and editing.

Data availability

Apart from the archival micrographs shown in Figure 2, which are available from the author on reasonable request, no new data were generated. All other material discussed is available in the cited published literature.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author used ChatGPT (OpenAI) to check the manuscript's conformity with the Journal's instructions for authors and to assist in verifying reference accuracy, Claude (Anthropic) to assist with literature searching and verification, reference management, and editorial revision of the text and preparation of the schematic figures, and Asta (Allen Institute for AI) for supplementary literature searching. After using these tools, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article. No generative or AI-based tool was used to create, colorize or alter any micrograph; Figure 2 was assembled from the original camera files, and Claude (Anthropic) was used only to scale and letter the panels.

Acknowledgements

The author thanks the co-authors of the 2011 report (A. Jianu, F. Pop, E. Guţu, S. Hostiuc and G. Curcă) for the autopsy and histopathological work from which the archival micrographs in Figure 2 derive.

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Received: September 22, 2026

Accepted: October 30, 2026