Myocardial Involvement in Patients With Histologically Diagnosed Cardiac Sarcoidosis: A Systematic Review and Meta-Analysis of Gross Pathological Images From Autopsy or Cardiac Transplantation Cases

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***Background*—**In patients with suspected cardiac sarcoidosis, late gadolinium enhancement on cardiovascular magnetic resonance imaging and/or ^{18}F-fluorodeoxyglucose uptake on positron emission tomography are often used to reach a clinical diagnosis of cardiac sarcoidosis. On the basis of data from the imaging literature of clinical cardiac sarcoidosis, no specific features of myocardial involvement are regarded as pathognomonic for cardiac sarcoidosis. Thus, a diagnosis of cardiac sarcoidosis is challenging to make. There has been no systematic analysis of histologically diagnosed cardiac sarcoidosis for patterns of myocardial involvement. We hypothesized that certain patterns of myocardial involvement are more frequent in histologically diagnosed cardiac sarcoidosis.

***Methods and Results*—**We performed a systematic review and meta-analysis of gross pathological images from the published literature of patients with histologically diagnosed cardiac sarcoidosis who underwent autopsy or cardiac transplantation. Thirty-three eligible articles provided images of 49 unique hearts. Analysis of these hearts revealed certain features of myocardial involvement in >90% of cases: left ventricular (LV) subepicardial, LV multifocal, septal, and right ventricular free wall involvement. In contrast, other patterns were seen in 0% to 6% of cases: absence of gross LV myocardial involvement, isolated LV midmyocardial involvement, isolated LV subendocardial involvement, isolated LV transmural involvement, absence of septal involvement, or isolated involvement of only one LV level.

***Conclusions*—**In this systematic review and meta-analysis of histologically diagnosed cardiac sarcoidosis, we identified certain features of myocardial involvement that occurred frequently and others that occurred rarely or never. These patterns could aid the interpretation of cardiovascular magnetic resonance imaging and positron emission tomography imaging and improve the diagnosis and the prognostication of patients with suspected cardiac sarcoidosis. **(*J Am Heart Assoc*. 2019;8:e011253. DOI: 10.1161/JAHA.118.011253.)**

Key Words: autopsy • cardiac sarcoidosis • cardiac transplantation • late gadolinium enhancement • myocardial structure • phenotype • prognosis

Sarcoidosis is a multisystem granulomatous disorder of unclear cause. The heart is involved in up to 25% of patients with sarcoidosis, and cardiac sarcoidosis is often associated with a poor prognosis.[1] Cardiovascular magnetic resonance imaging (CMR) is frequently used in the evaluation of patients with suspected cardiac sarcoidosis, and myocardial involvement identified as late gadolinium enhancement (LGE) is incorporated in the various diagnostic criteria used to make the diagnosis of cardiac sarcoidosis.[2–6] Similarly, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography is also often used in the evaluation and monitoring of patients with suspected cardiac sarcoidosis, with active myocardial involvement identified as ^{18}F-FDG uptake.[2–6]

Patel et al first described diverse patterns of LGE in patients with extracardiac biopsy-proven sarcoidosis.[7] Although 86% (18/21) of patients with LGE in the study had at least one region with LGE in a nonischemic pattern, subendocardial LGE typical for coronary artery disease was also noted as representing cardiac sarcoidosis in the absence of obstructive coronary artery disease. This study was the basis of statements

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Accompanying Figures S1 and S49 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011253

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Clinical Perspective

What Is New?

- We performed a systematic analysis and meta-analysis of histologically diagnosed cardiac sarcoidosis for patterns of myocardial involvement using gross pathological images from autopsy or cardiac transplantation cases.
- Certain features of myocardial involvement were seen in >90% of cases: left ventricular (LV) subepicardial, LV multifocal, septal, and right ventricular free wall involvement.
- Other patterns were seen in 0% to 6% of cases: absence of gross myocardial involvement, isolated LV midmyocardial involvement, isolated LV subendocardial involvement, isolated LV transmural involvement, absence of septal involvement, or isolated involvement of only one LV level.

What Are the Clinical Implications?

- These patterns of myocardial involvement in cardiac sarcoidosis could aid the interpretation of cardiovascular magnetic resonance imaging and ^{18}F-fluorodeoxyglucose positron emission tomography imaging and improve the diagnosis and the prognostication of patients with suspected cardiac sarcoidosis.

in the 2014 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis that "there is no specific pattern of LGE that is pathognomonic for cardiac sarcoidosis" and ". . .even a pattern that is typical for prior myocardial infarction can also represent cardiac sarcoidosis."[3] The lack of a specific LGE pattern for cardiac sarcoidosis makes it challenging to make the diagnosis.[8] This is an important issue as patient management is often guided by clinical diagnoses rather than histological diagnoses because an endomyocardial biopsy is deemed to have limited sensitivity to detect cardiac sarcoidosis.[3] Although the presence of frequent LGE patterns in cardiac sarcoidosis has been suggested,[9,10] there has been no systematic analysis of patterns of myocardial involvement in cardiac sarcoidosis, especially in histologically diagnosed cardiac sarcoidosis. We hypothesized that certain patterns of myocardial involvement are more frequent in histologically diagnosed cardiac sarcoidosis.

To determine patterns of myocardial involvement in cardiac sarcoidosis, we performed a systematic review and meta-analysis of published gross pathological images of the heart from patients with histologically diagnosed cardiac sarcoidosis.

Methods

All data supporting the findings are provided within the article. We studied gross pathological images of hearts from either patients who underwent a autopsy or those who had heart transplantation for cardiac sarcoidosis and had a definitive histological diagnosis of cardiac sarcoidosis. Patients who underwent a autopsy died from either sudden cardiac death attributed to cardiac sarcoidosis or other causes directly related to cardiac sarcoidosis (eg, multiorgan failure after recurrent ventricular arrhythmias attributed to cardiac sarcoidosis). We chose to specifically study these patients because they experienced the major adverse cardiac events that we aim to avoid in patients with suspected cardiac sarcoidosis.

Search Strategy

We searched the PubMed, Embase, and Cochrane databases in March 2018 to perform a systematic review of peer-reviewed publications that included gross pathological images of hearts taken from patients who either died from cardiac sarcoidosis or underwent heart transplantation for cardiac sarcoidosis. Search terms used were as follows: "cardiac sarcoidosis and pathology," "cardiac sarcoidosis and autopsy," "cardiac sarcoidosis and autopsy," and "cardiac sarcoidosis and explant."

Study Selection

Two investigators (O.O. and C.S.) independently scanned all titles and abstracts and obtained full-text reports of articles that indicated or suggested eligibility. The full-text articles were then assessed for eligible gross heart pathological images by the same investigators independently. We included images from patients who either died of causes related to cardiac sarcoidosis or underwent heart transplantation for cardiac sarcoidosis and had a histological diagnosis of cardiac sarcoidosis based on the presence of noncaseating granulomas. We excluded gross pathological images when the myocardium could not be assessed in at least 6 of 17 American Heart Association left ventricular (LV) segments[11] because of either anatomical sections performed or poor image quality.

Data Collection

To identify features of myocardial involvement in patients with cardiac sarcoidosis, 2 investigators (O.O., F.K.) independently recorded the following 5 domains of myocardial damage features from the gross pathological images:

1. Location of involvement within the LV wall:
   - Subepicardial (involvement of the outer portion, including the right ventricular [RV] aspect of the interventricular septum);
   - Midmyocardial (involvement of the middle portion);

- Subendocardial (involvement of the inner portion);
- Transmural (involvement of the entire thickness of the wall).

2. Focality within the LV:

- Unifocal (1 single lesion);
- Multifocal (>1 discrete lesion).

3. LV segments involved:

- Anterior segments;
- Septal segments;
- Inferior segments;
- Lateral segment.

4. LV levels involved:

- Basal LV;
- Mid LV;
- Apical LV.

5. Involvement of the RV free wall

- Yes;
- No.

Discordances were resolved after consensus with a third investigator (C.S.). Within each domain, the prevalence of various features of myocardial involvement was compared. Features that were either frequently (>90%) or rarely (<10%) present were identified.

Statistical Analysis

Categorical variables were expressed as counts with percentages. χ^2 Tests were used to compare discrete data between groups; in those cases in which the expected cell count was <5, the Fisher exact test was used. Statistical analyses were performed using R, version 3.3.3 (The R Foundation; https://www.r-project.org/). All statistical tests were 2 tailed, and $P<0.05$ was considered statistically significant.

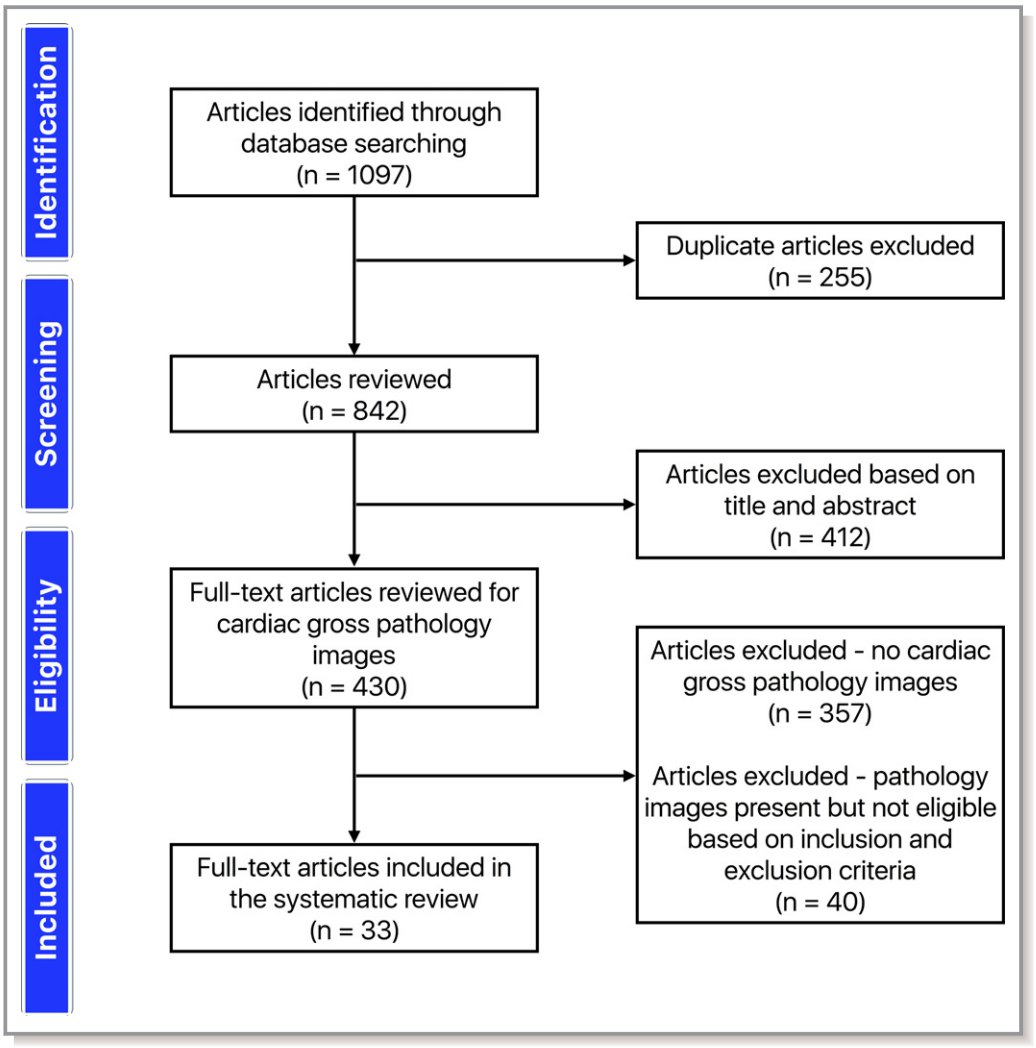

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the flow of information through the different phases of the systematic review.

Table 1. Articles and Gross Pathological Images of Cardiac Sarcoidosis Included in the Study

Figure	Article No.	Author and Year of Publication	Figure No. Within Article	Autopsy or Explant	Cause of Death	No. of LV Segments Seen
S1	1	Fawcett and Goldberg, 1974[12]	1	Autopsy	Sudden cardiac death	6
S2	2	Fleming, 1974[13]	4	Autopsy	Sudden cardiac death	6
S3	2	Fleming, 1974[13]	9	Autopsy	Sudden cardiac death	6
S4	3	Roberts et al, 1977[14]	5	Autopsy	Sudden cardiac death	6
S5	4	James and Pounder, 1982[15]	1	Autopsy	Sudden cardiac death	6
S6	5	(Authors not listed), 1990[16]	9	Autopsy	Cardiogenic shock	6
S7	6	Antecol and Roberts, 1990[17]	5	Autopsy	Sudden cardiac death	12
S8	7	Shirani and Roberts, 1993[18]	4	Autopsy	Sudden cardiac death	17
S9	7	Shirani and Roberts, 1993[18]	5	Autopsy	Sudden cardiac death	6
S10	8	Donsky et al, 2002[19]	2	Explant	. . .	17
S11	9	Wan Muhaizan et al, 2004[20]	2	Autopsy	Cardiogenic shock	16
S12	10	Goyal and Aragam, 2006[21]	1	Explant	. . .	6
S13	11	Halushka et al, 2006[22]	1	Explant	. . .	6
S14	12	Hamilton et al, 2007[23]	1	Autopsy	Sudden cardiac death	6
S15	13	Morikawa et al, 2008[24]	2	Autopsy	Hemorrhagic shock	6
S16	14	Luk et al, 2009[25]	2	Explant	. . .	6
S17	15	Riezzo et al, 2009[26]	2	Autopsy	Sudden cardiac death	6
S18	16	Roberts et al, 2009[27]	2	Explant	. . .	17
S19	16	Roberts et al, 2009[27]	3	Explant	. . .	17
S20	16	Roberts et al, 2009[27]	4	Explant	. . .	12
S21	17	Sharma et al, 2009[28]	1, 2	Autopsy	Sudden cardiac death	17
S22	18	Tavora et al, 2009[29]	2	Autopsy	Sudden cardiac death	6
S23	18	Tavora et al, 2009[29]	2	Autopsy	Sudden cardiac death	6
S24	18	Tavora et al, 2009[29]	3	Autopsy	Sudden cardiac death	17
S25	18	Tavora et al, 2009[29]	7	Autopsy	Sudden cardiac death	6
S26	19	Dubrey and Falk, 2010[30]	2	Explant	. . .	6
S27	20	Lagana et al, 2010[31]	1	Explant	. . .	6
S28	21	Bagwan et al, 2011[32]	1	Autopsy	Sudden cardiac death	6
S29	22	Strauss et al, 2011[33]	2	Explant	. . .	6
S30	23	Armstrong, 2013[34]	2	Autopsy	Sudden cardiac death	6
S31	24	Zacek et al, 2013[35]	2	Autopsy	Cardiogenic shock	6
S32	25	Lynch et al, 2014[36]	1	Autopsy	Sudden cardiac death	6
S33	26	Roberts et al, 2014a[37]	1	Explant	. . .	17
S34	26	Roberts et al, 2014[37]	2	Explant	. . .	17
S35	26	Roberts et al, 2014[37]	3	Explant	. . .	17
S36	26	Roberts et al, 2014[37]	4	Explant	. . .	17
S37	26	Roberts et al, 2014[37]	5	Explant	. . .	12
S38	27	Roberts et al, 2014[38]	27	Explant	. . .	17
S39	28	Armstrong et al, 2015[39]	1	Explant	. . .	17
S40	28	Armstrong et al, 2015[39]	3	Explant	. . .	17

Continued

Table 1. Continued

Figure	Article No.	Author and Year of Publication	Figure No. Within Article	Autopsy or Explant	Cause of Death	No. of LV Segments Seen
S41	29	Jeudy et al, 2015[40]	2	Autopsy	Sudden cardiac death	6
S42	29	Jeudy et al, 2015[40]	3	Explant	. . .	6
S43	29	Jeudy et al, 2015[40]	4	Explant	. . .	6
S44	30	Kajimoto et al, 2015[41]	2	Autopsy	Hemorrhagic shock	17
S45	31	Vasaturo et al, 2015[42]	1	Autopsy	Toxic shock syndrome	16
S46	32	Di Gesaro et al, 2016[43]	2	Explant	. . .	17
S47	33	Roberts et al, 2018[44]	2	Explant	. . .	6
S48	33	Roberts et al, 2018[44]	2	Explant	. . .	6
S49	33	Roberts et al, 2018[44]	2	Explant	. . .	6

LV indicates left ventricular.

Results

The systematic review yielded 33 articles[12–44] published in the peer-reviewed literature between 1974 and March 2018 (Figure 1). The 33 articles provided gross pathological images of 49 unique hearts with cardiac sarcoidosis: 25 were from autopsy examinations, and 24 were explanted for heart transplantation (Table 1). All heart transplantations occurred for cardiac sarcoidosis, and of the 25 hearts from autopsy examinations, 18 (72%) had sudden death and 7 (28%) died of immediate causes other than sudden death but cardiac sarcoidosis directly contributed to the death. Five representative examples[17,24,29,39,44] with details of features of myocardial involvement are reproduced in Figure 2. All 49 gross pathological images are reproduced with permission in Figures S1 through S49.

Prevalence of Features of Myocardial Involvement

Location of involvement within the LV wall

Within the LV wall, the involvement was subepicardial in 98% of cases, with significantly lower midmyocardial (65.3%), subendocardial (53.1%), or transmural (63.3%) involvement ($P<0.05$ for all) (Tables 2 and 3).

Focality within the LV

Multifocal LV involvement was significantly more common than unifocal involvement (93.9% versus 6.1%; $P<0.05$).

LV segments involved

The septal segments were involved in 98% of cases, with significantly lower involvement of the anterior (75.0%), lateral (71.4%), and inferior (82.5%) segments ($P<0.05$ for all).

LV levels involved

The basal and mid LV were almost always involved (97.5% and 100%, respectively), and the apical LV was less often involved when compared with either basal or mid LV (80.8%; $P<0.05$ for both comparisons). However, the difference was not significant when comparisons were made only using the 26 patients who had pathological images of all LV levels.

Involvement of the RV free wall

The RV free wall was involved in 90.7% of cases.

Rare Features of Myocardial Involvement

On the basis of the above, we identified a list of rare features (Table 4). These features had a prevalence of <6%, and many were never present. There were no patients without gross LV myocardial involvement. LV midmyocardial or subendocardial involvement without subepicardial involvement was never present. LV transmural involvement without separate subepicardial involvement was present in only 1 patient (2.0%). Unifocal involvement was present in only 6.1% of patients. Absence of septal involvement was noted in only 1 patient (2.0%). In terms of the levels of involvement, isolated involvement of only one LV level was seen in only 1 patient (2.0%) for the basal level and 0 patients for the mid and apical levels.

Discussion

In this systematic review and meta-analysis of gross pathological images of hearts from patients with histologically diagnosed cardiac sarcoidosis who underwent either autopsy or heart transplantation for cardiac sarcoidosis, we identified frequent and rare features of myocardial involvement. LV

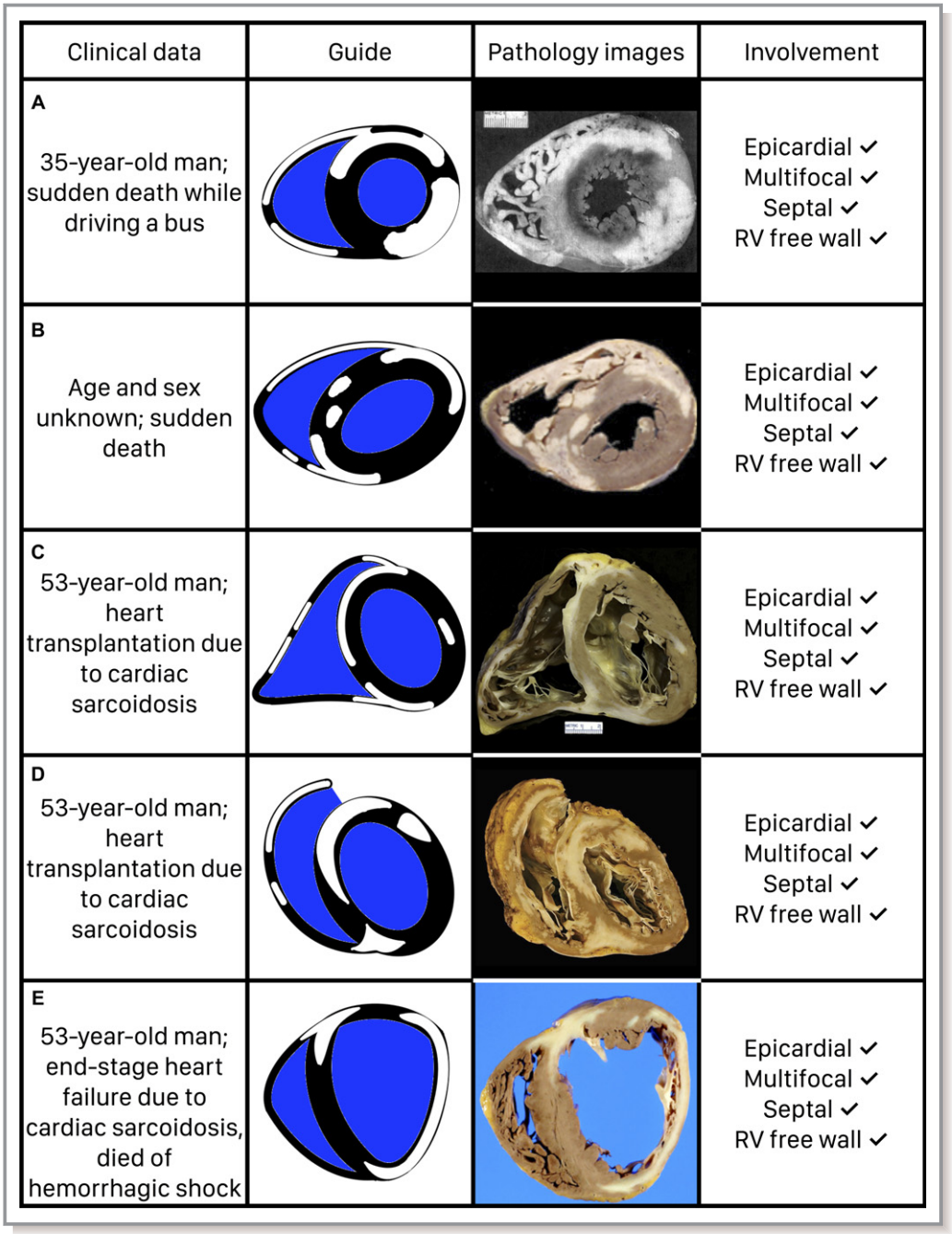

Figure 2. Illustrated examples of 5 gross pathological images from the study, demonstrating frequent features of myocardial involvement in cardiac sarcoidosis, are shown. **A**, Image is reprinted from Antecol and Roberts[17] with permission. Copyright © 1990, Elsevier. **B**, Image is reprinted from Tavora et al[29] with permission. Copyright © 2009, Elsevier. **C**, Image is reprinted from Armstrong et al[39] with permission. Copyright © 2013, Wolters Kluwer Health, Inc. **D**, Image is reprinted from Roberts et al[44] with permission. Copyright © 2018, American Medical Association. **E**, Image is reprinted from Morikawa et al[24] with permission. Copyright © 2008, Elsevier. RV indicates right ventricular.

subepicardial, LV multifocal, septal, and RV free wall involvement were frequent (present in >90% of patients) features. On the other hand, lack of gross LV myocardial, isolated LV midmyocardial, or isolated LV subendocardial involvement was never present. Similarly, isolated LV transmural involvement, absence of septal involvement, and isolated involvement of only one LV level were rare (present in 2% of patients) features.

One of the key strengths of our data is that they are derived only from patients with histologically diagnosed cardiac sarcoidosis. The contemporary understanding of myocardial involvement in cardiac sarcoidosis, in which no

Table 2. Features of Myocardial Involvement in Cardiac Sarcoidosis on Gross Pathological Images

Figure	Subepicardial LV Involvement	Midmyocardial LV Involvement	Subendocardial LV Involvement	Transmural LV Involvement	Multifocal LV Involvement	Septal LV Involvement	Lateral LV Involvement	Anterior LV Involvement	Inferior LV Involvement	Basal LV Involvement	Mid-LV Involvement	Apical LV Involvement	RV Free Wall
S1	Yes	Yes	Yes	No	Yes	Yes	Yes	. . .	. . .	Yes	Yes	Yes	. . .
S2	Yes	No	Yes	Yes	Yes	Yes	No	. . .	. . .	Yes	Yes	Yes	Yes
S3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	Yes	Yes	Yes	. . .
S4	Yes	Yes	No	Yes	Yes	Yes	No	. . .	. . .	Yes	Yes	No	No
S5	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	Yes	. . .	Yes
S6	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	. . .	Yes	. . .	Yes
S7	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	Yes
S8	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S9	Yes	Yes	No	No	Yes	Yes	Yes	. . .	. . .	Yes	Yes	Yes	Yes
S10	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
S11	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
S12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	Yes	Yes	Yes	Yes
S13	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes	. . .	. . .	Yes
S14	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	. . .
S15	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	Yes
S16	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	Yes
S17	Yes	No	Yes	No	Yes	Yes	Yes	. . .	. . .	Yes	Yes	No	. . .
S18	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
S19	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S20	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Yes	. . .	Yes
S21	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S22	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	No
S23	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S24	Yes	No	No	No	No	Yes	No	No	No	. . .	Yes	. . .	Yes
S25	Yes	No	No	Yes	No	Yes	No	No	Yes	. . .	Yes	. . .	Yes
S26	Yes	Yes	No	Yes	Yes	Yes	Yes	. . .	. . .	Yes	Yes	Yes	Yes
S27	Yes	Yes	No	Yes	Yes	Yes	No	. . .	. . .	Yes	Yes	No	Yes
S28	Yes	Yes	No	No	Yes	Yes	No	Yes	No	. . .	Yes	. . .	No
S29	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	. . .	Yes	. . .	. . .
S30	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	. . .	. . .	Yes

Continued

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Table 2. Continued

Figure	Subepicardial LV Involvement	Midmyocardial LV Involvement	Subendocardial LV Involvement	Transmural LV Involvement	Multifocal LV Involvement	Septal LV Involvement	Lateral LV Involvement	Anterior LV Involvement	Inferior LV Involvement	Basal LV Involvement	Mid-LV Involvement	Apical LV Involvement	RV Free Wall
S31	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	. . .	. . .	Yes
S32	Yes	Yes	No	No	Yes	Yes	Yes	No	No	. . .	Yes	. . .	No
S33	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
S34	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S35	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S36	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S37	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	Yes
S38	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S39	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S40	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S41	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	Yes
S42	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	. . .	Yes	. . .	Yes
S43	Yes	No	No	No	No	Yes	No	Yes	No	. . .	Yes	. . .	. . .
S44	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S45	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes
S46	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
S47	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	. . .	. . .	Yes
S48	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	Yes
S49	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	. . .	. . .	Yes

LV indicates left ventricular; RV, right ventricular.

Table 3. Prevalence of Features of Myocardial Involvement in Cardiac Sarcoidosis

Feature of Myocardial Involvement	Prevalence, No./Total (%)
LV subepicardial involvement (any)	48/49 (98.0)
LV midmyocardial involvement (any)	32/49 (65.3)
LV subendocardial involvement (any)	26/49 (53.1)
LV transmural involvement (any)	31/49 (63.3)
LV multifocal involvement	46/49 (93.9)
Septal segment involvement (any)	48/49 (98.0)
LV lateral segment involvement (any)	35/49 (71.4)
LV anterior segment involvement (any)	30/40 (75.0)
LV inferior segment involvement (any)	33/40 (82.5)
Basal LV involvement (any)	39/40 (97.5)
Mid-LV involvement (any)	38/38 (100.0)
Apical LV involvement (any)	21/26 (80.8)
RV free wall involvement (any)	39/43 (90.7)

LV indicates left ventricular; RV, right ventricular.

specific patterns are believed to be pathognomonic for cardiac sarcoidosis, is largely based on LGE CMR data,[7] which include patients with clinical but not histologically diagnosed cardiac sarcoidosis. In these studies, a clinical diagnosis of cardiac sarcoidosis is reached after excluding other explanations for the LGE,[3] which may not always be accurate. For instance, coronary artery disease as the cause for subendocardial LGE in patients with suspected cardiac sarcoidosis is typically excluded by the absence of obstructive coronary artery disease on coronary angiography.[7] However, this does not exclude the possibility of myocardial infarction with nonobstructive coronary arteries.[45,46]

Table 4. Rare Features of Myocardial Involvement in Cardiac Sarcoidosis

Feature of Myocardial Involvement	Prevalence, No./Total (%)
No gross LV involvement	0/49 (0.0)
No LV subepicardial involvement	1/49 (2.0)
LV midmyocardial involvement without subepicardial involvement	0/49 (0.0)
LV subendocardial involvement without subepicardial involvement	0/49 (0.0)
LV transmural involvement without separate subepicardial involvement	1/49 (2.0)
LV unifocal involvement	3/49 (6.1)
No septal wall involvement	1/49 (2.0)
LV lateral wall involvement without septal wall involvement	1/49 (2.0)
No LV basal involvement	1/26 (3.8)*
No LV mid involvement	0/26 (0.0)*
Apical LV involvement without basal or mid LV involvement	0/26 (0.0)*

LV indicates left ventricular.
*A total of 26 patients had images of the basal, mid, and apical LV.

Our data demonstrate that there are characteristic features of myocardial involvement in cardiac sarcoidosis. These features could be used to identify patients with cardiac sarcoidosis using LGE CMR and ^{18}F-FDG positron emission tomography, particularly those in whom cardiac sarcoidosis was not suspected before the imaging study. More important, these data imply that patients with LGE or ^{18}F-FDG uptake in patterns that were never or rarely present in this systematic review could have an alternate explanation for the imaging findings. For instance, isolated subendocardial LGE may represent a myocardial infarction, and in the absence of coronary artery disease, it may still represent myocardial infarction with nonobstructive coronary arteries, rather than cardiac sarcoidosis. Similarly, ^{18}F-FDG uptake isolated to the lateral wall may represent inadequate suppression of physiological uptake rather than true cardiac sarcoidosis.[47]

Limitations

Our systematic review and meta-analysis is based on the published pathological literature, which introduces bias. Only a third of cases had 16 or 17 segments included in the gross pathological images, which raises the possibility that some of the features of myocardial involvement could have been missed. Cases included in the publications represent the most impressive cases and may not be representative of the entire spectrum of pathologically identified myocardial involvement in cardiac sarcoidosis. Similarly, our systematic review focuses on end-stage cardiac sarcoidosis (ie, those who either died of cardiac sarcoidosis or underwent heart transplantation because of it). Thus, it could be argued that our data do not include features of early myocardial involvement in cardiac sarcoidosis. However, our cases represent the adverse outcomes that we aim to avoid in patients with suspected cardiac sarcoidosis (ie, cardiac death and heart transplantation). Therefore, our data may carry prognostic implications. Studies are ongoing using these patterns of myocardial involvement on LGE CMR or ^{18}F-FDG to risk stratify patients with suspected cardiac sarcoidosis.

Conclusions

Myocardial involvement in end-stage cardiac sarcoidosis involves frequent (LV subepicardial, LV multifocal, septal, and RV free wall involvement) and rare (lack of gross LV myocardial involvement, isolated LV midmyocardial involvement, isolated

LV subendocardial involvement, isolated LV transmural involvement, absence of septal involvement, or isolated involvement of only one LV level) features. These patterns could be used to improve diagnosis and prognostication of suspected cardiac sarcoidosis with noninvasive imaging modalities, such as LGE CMR and ^{18}F-FDG positron emission tomography.

Disclosures

None.

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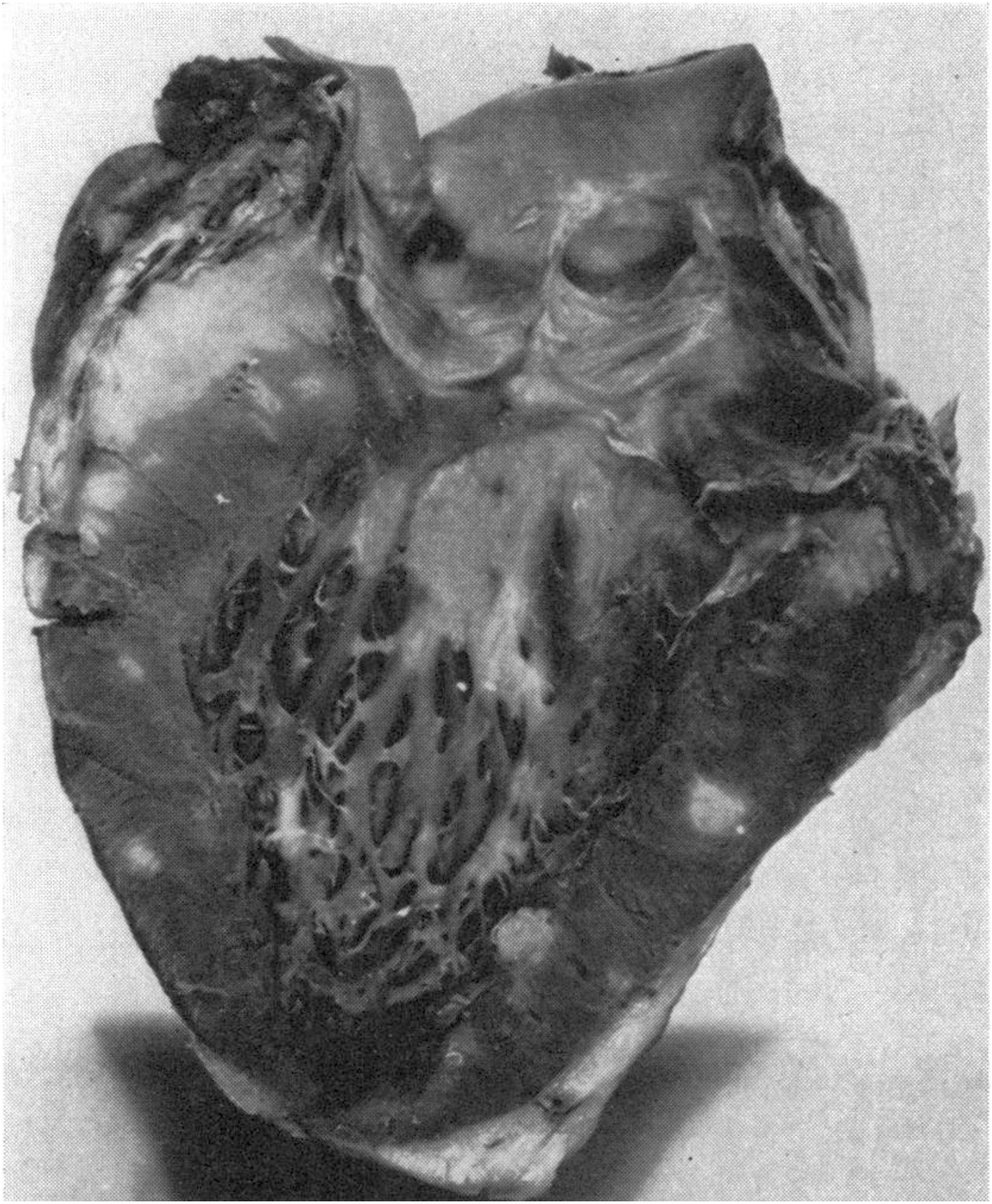

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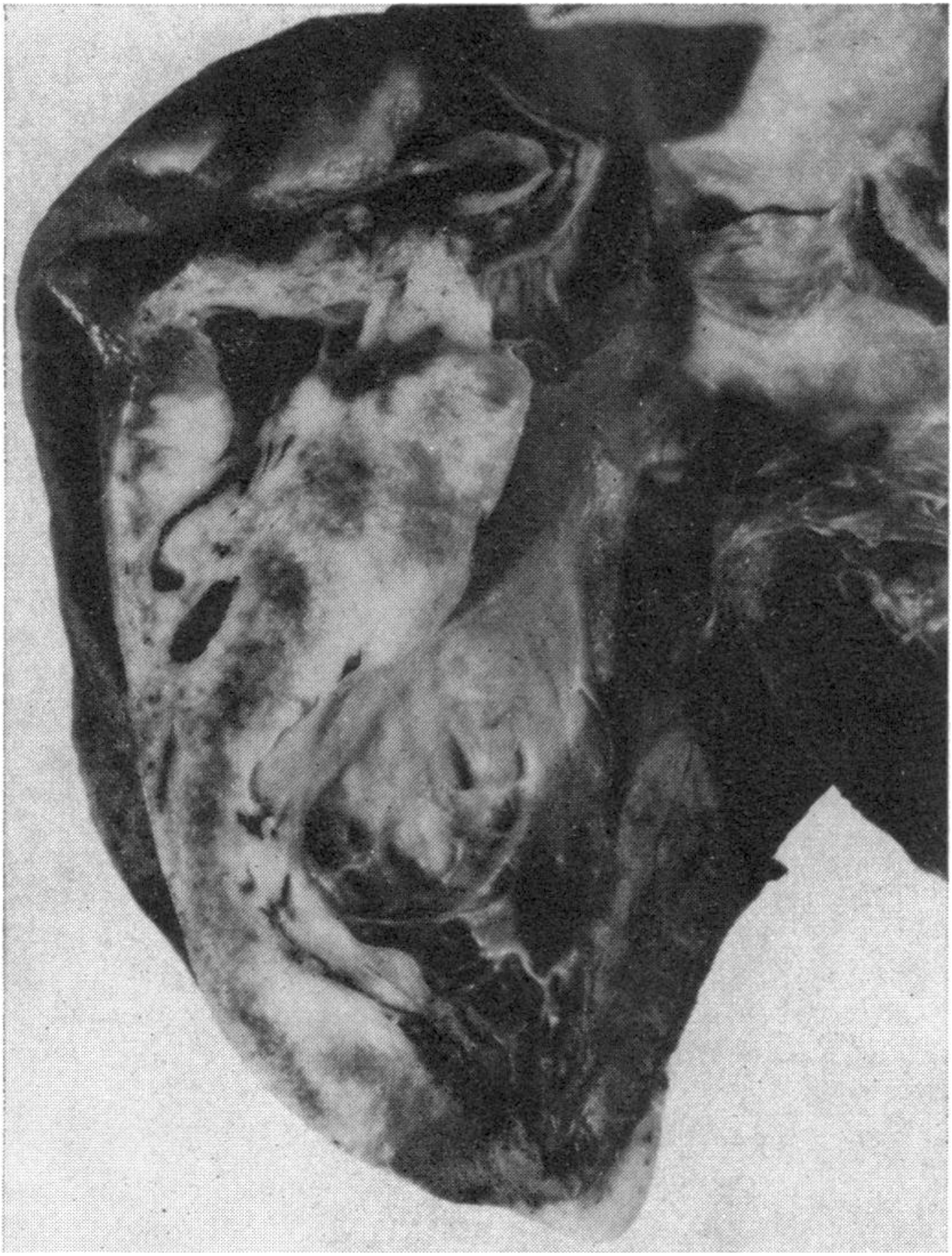

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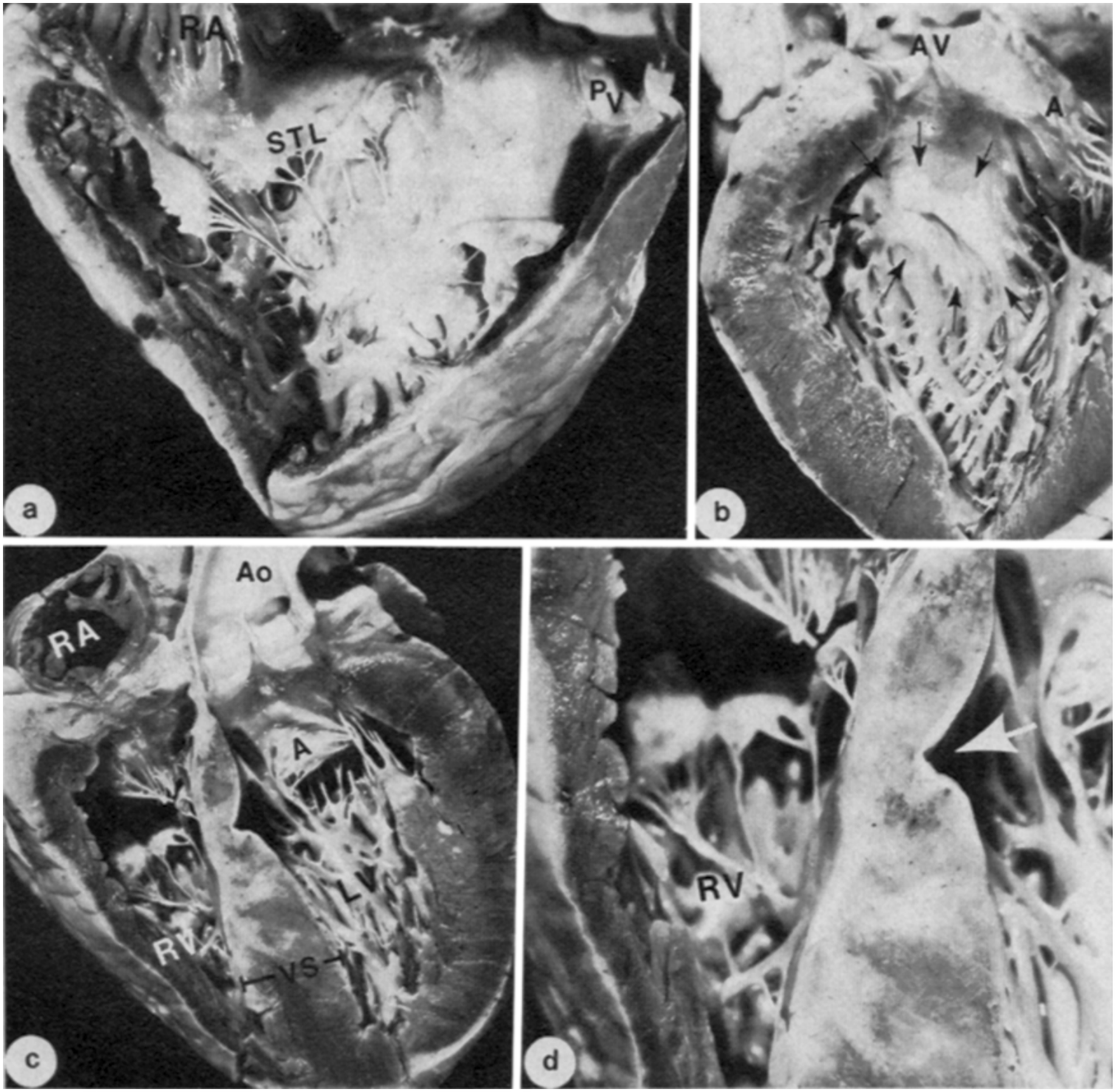

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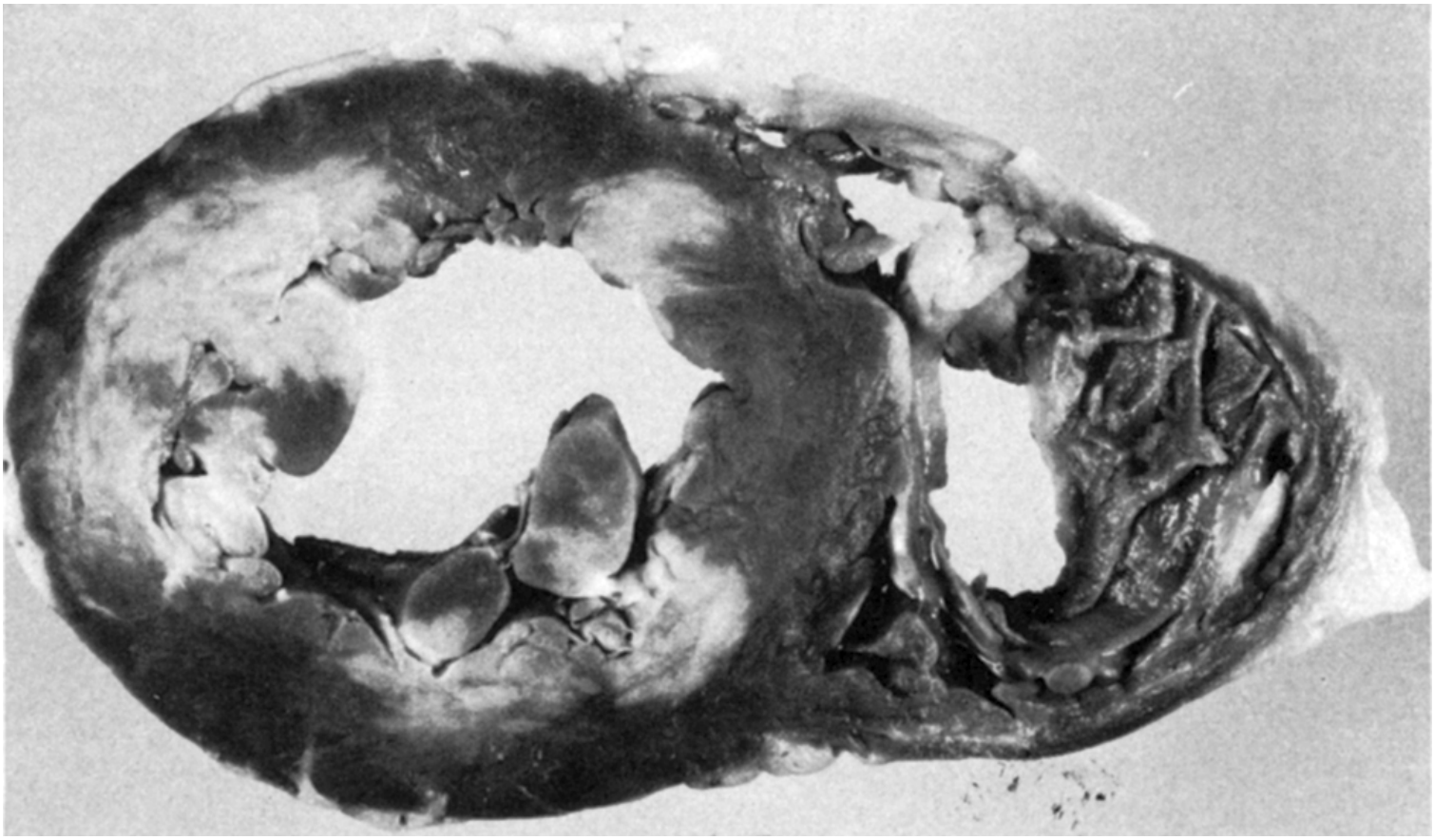

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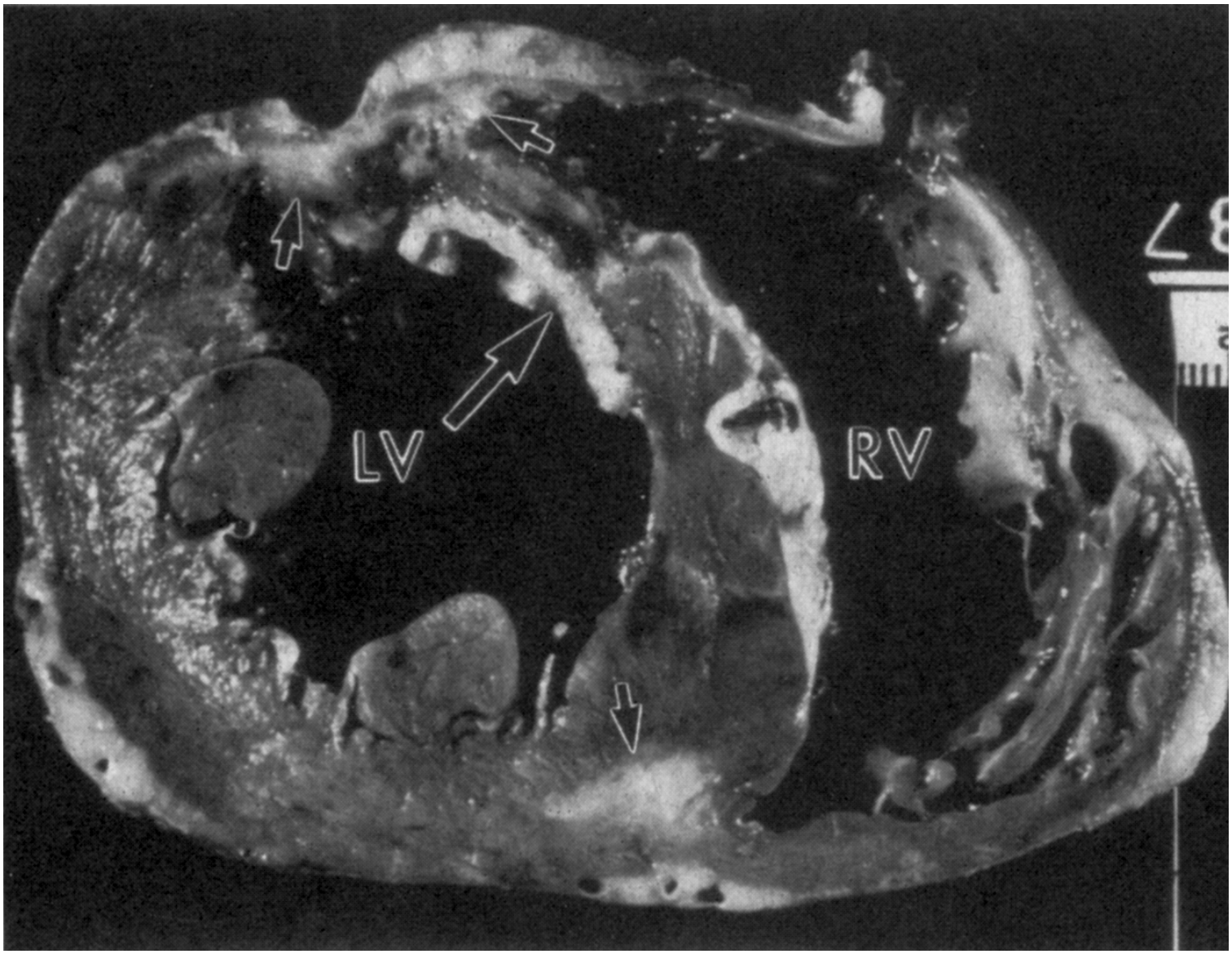

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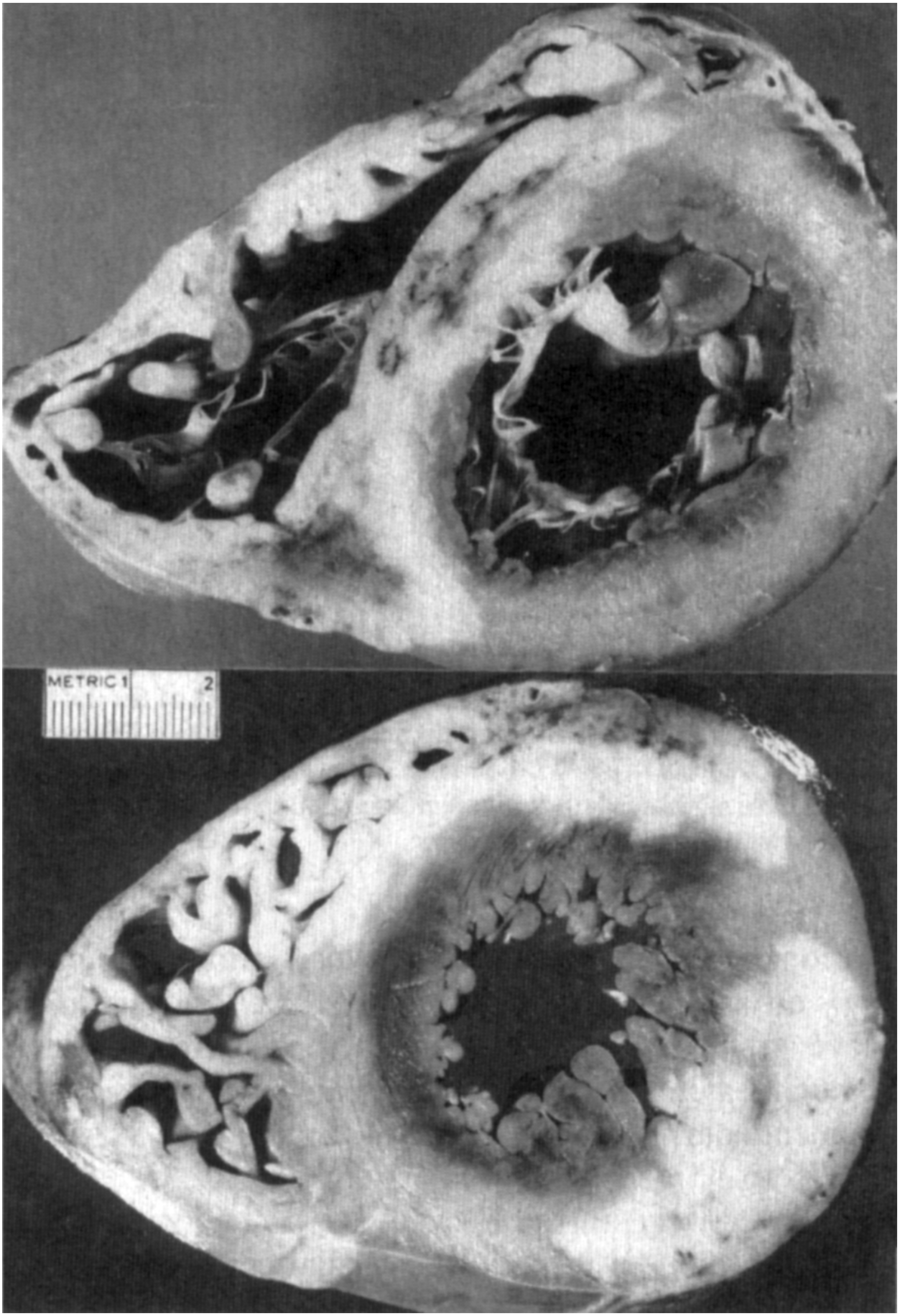

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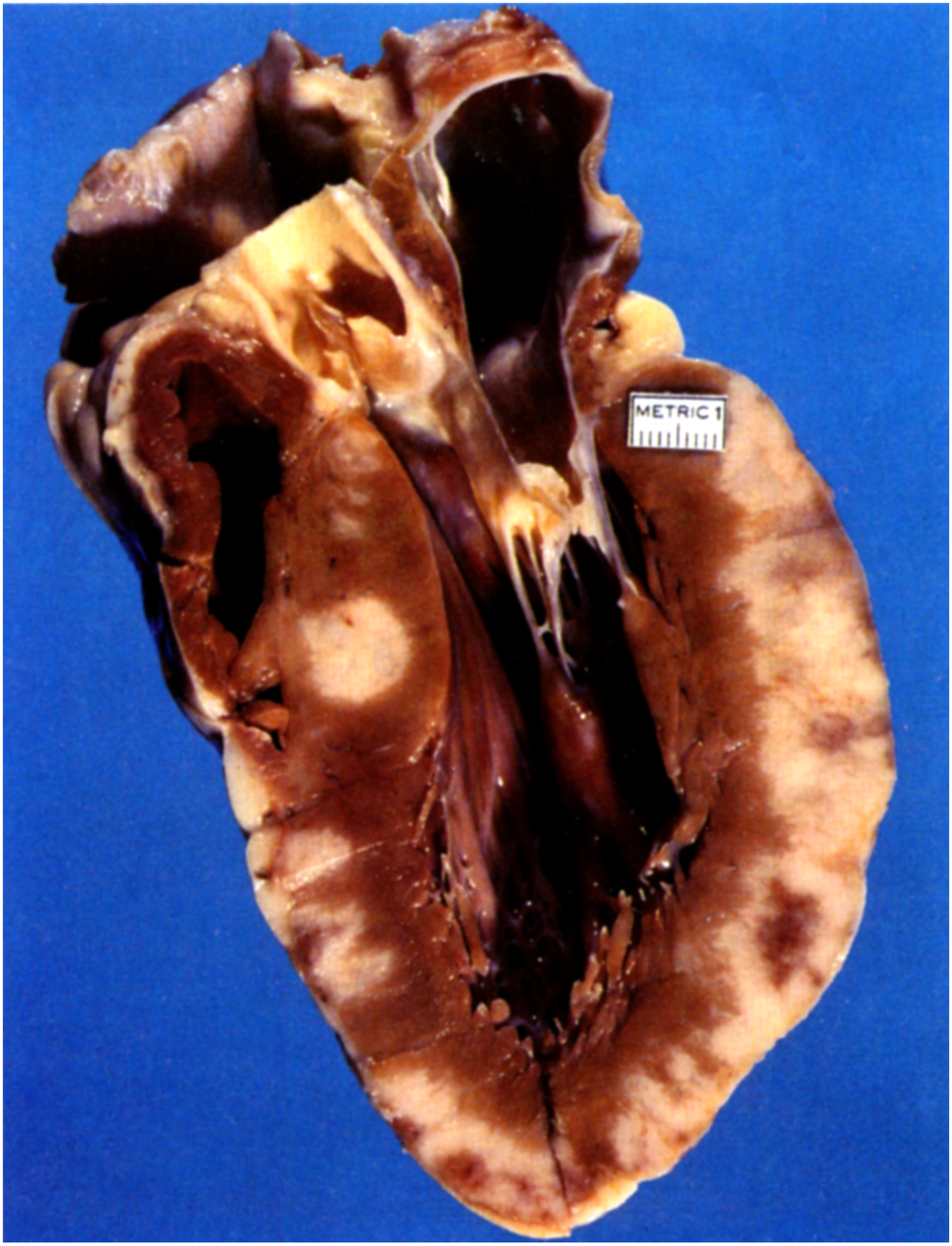

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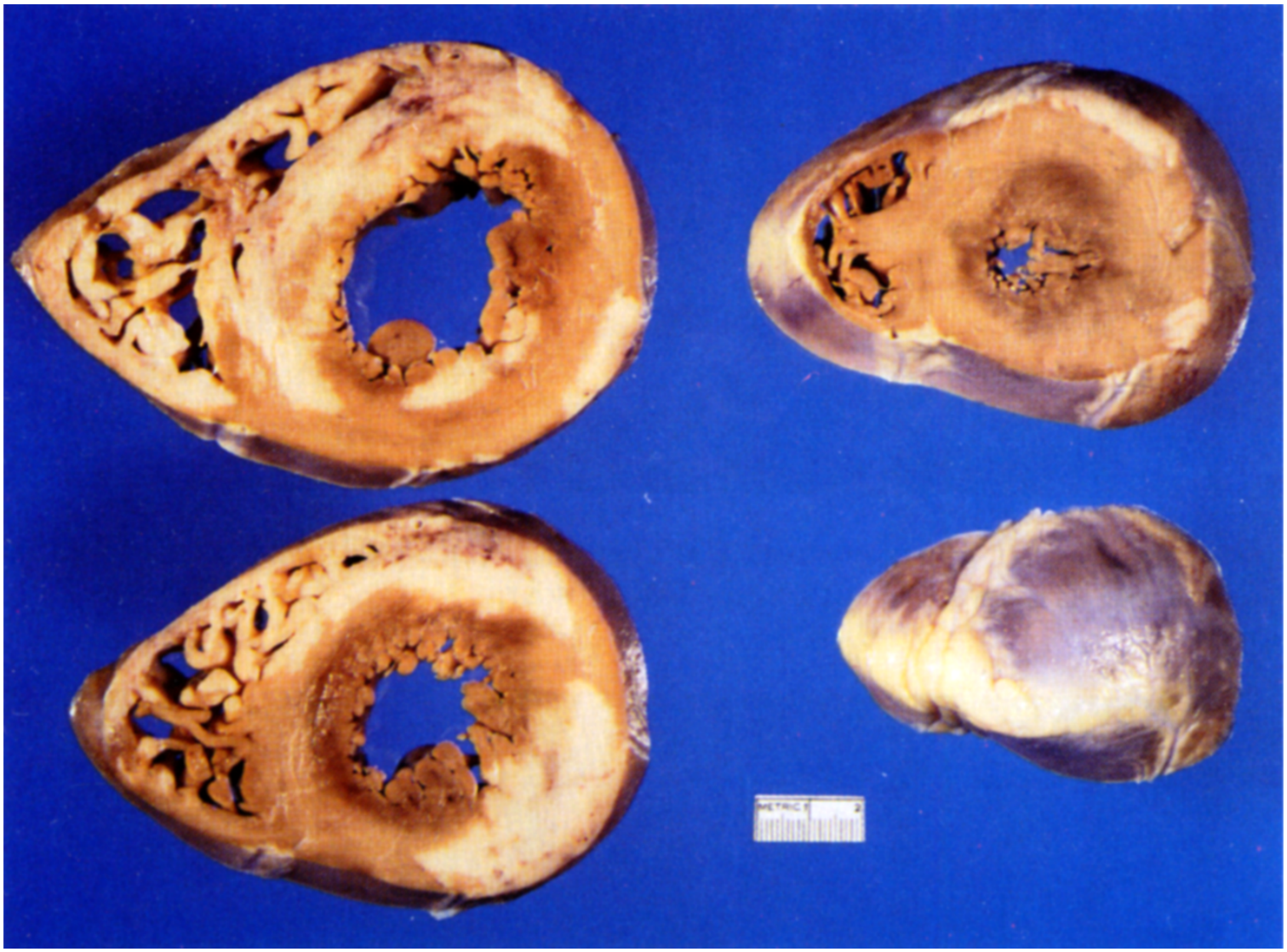

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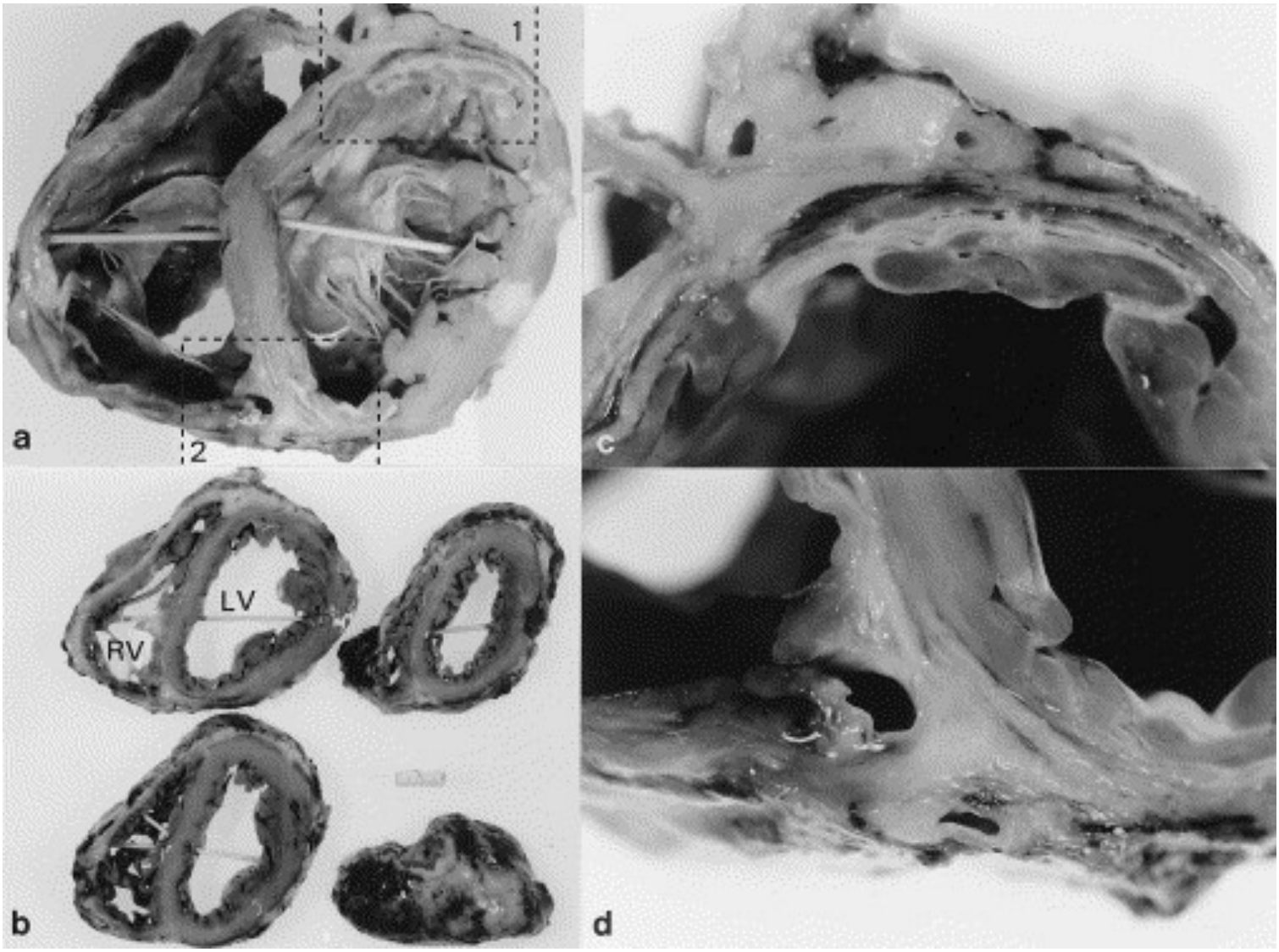

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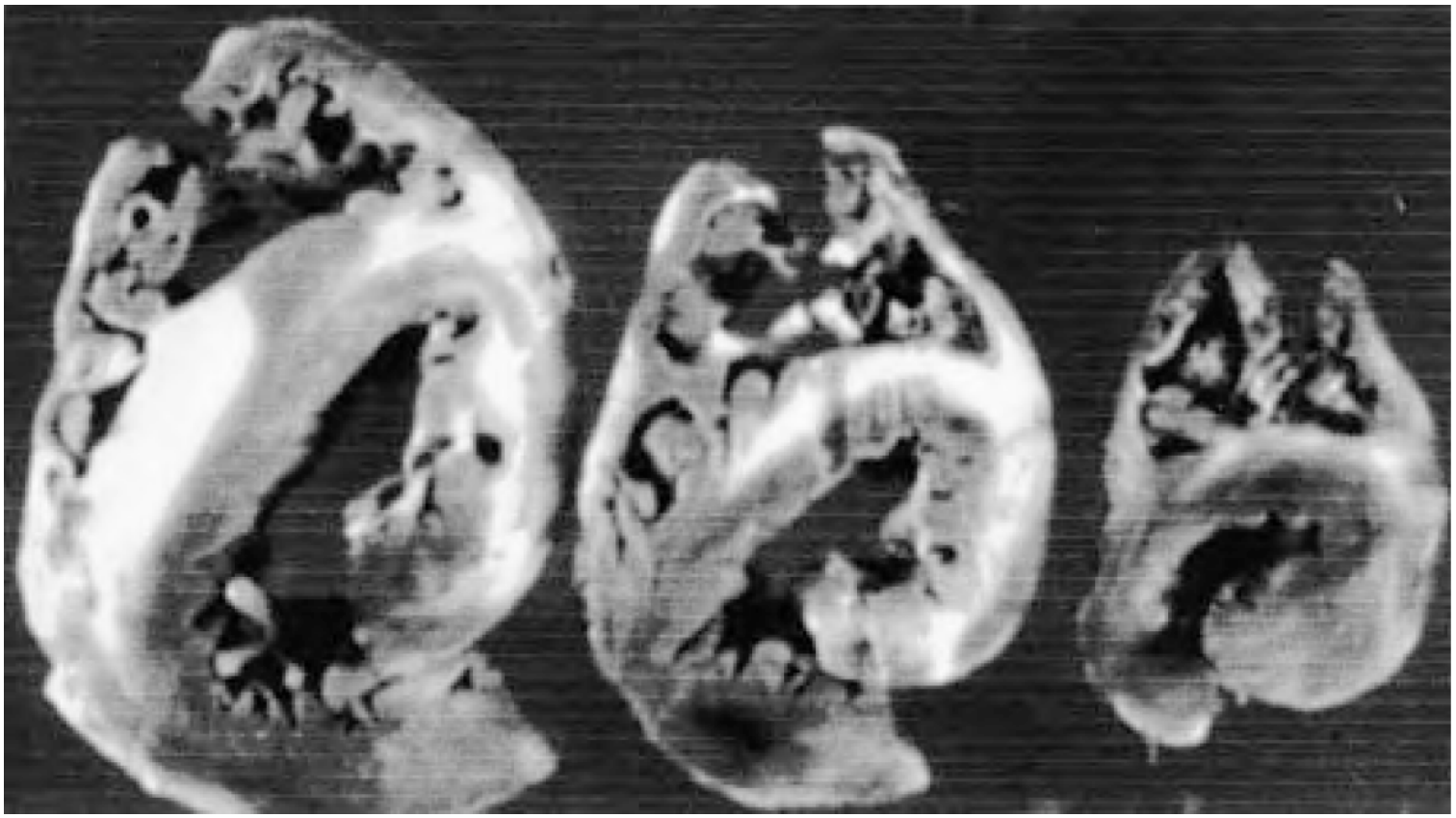

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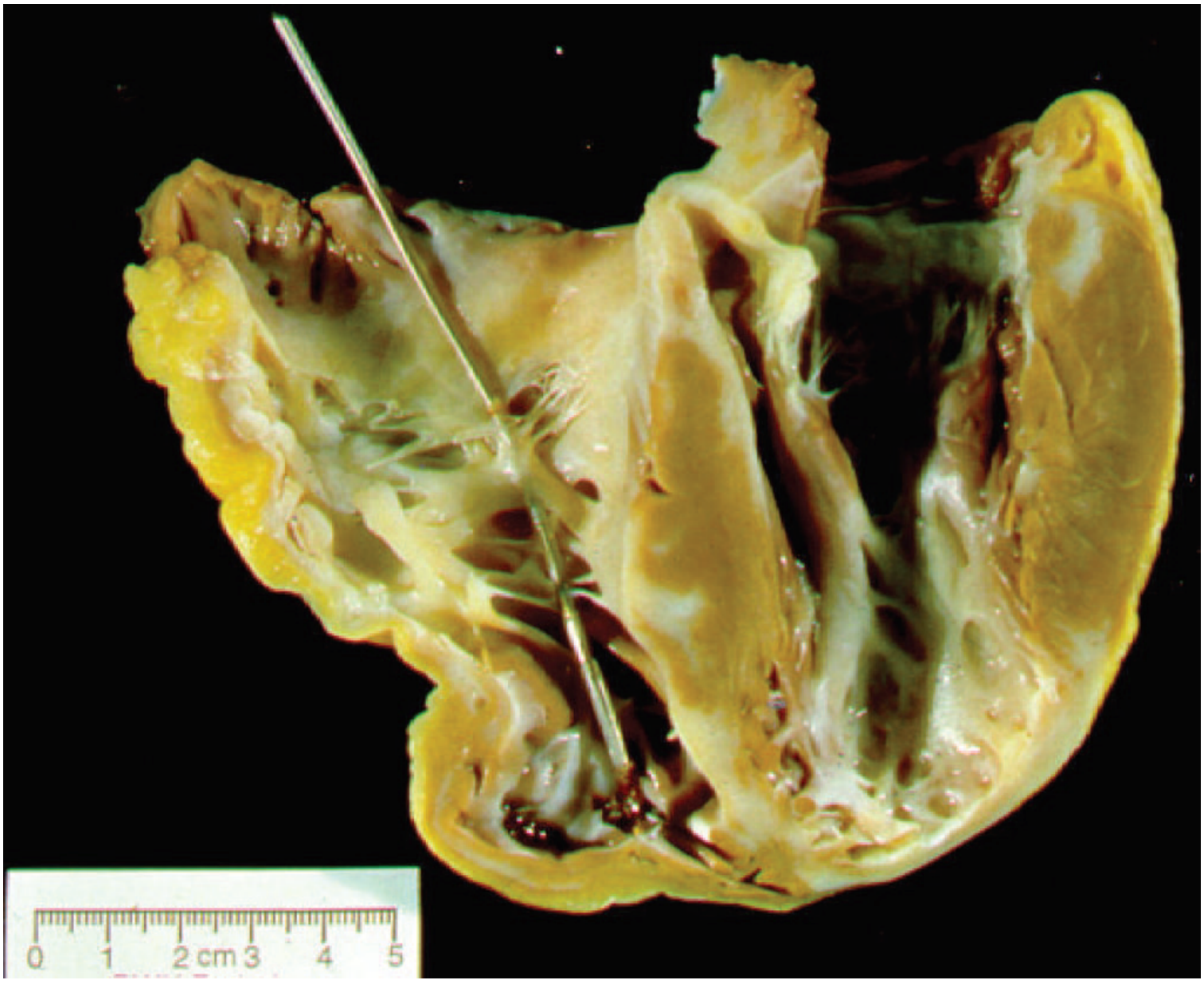

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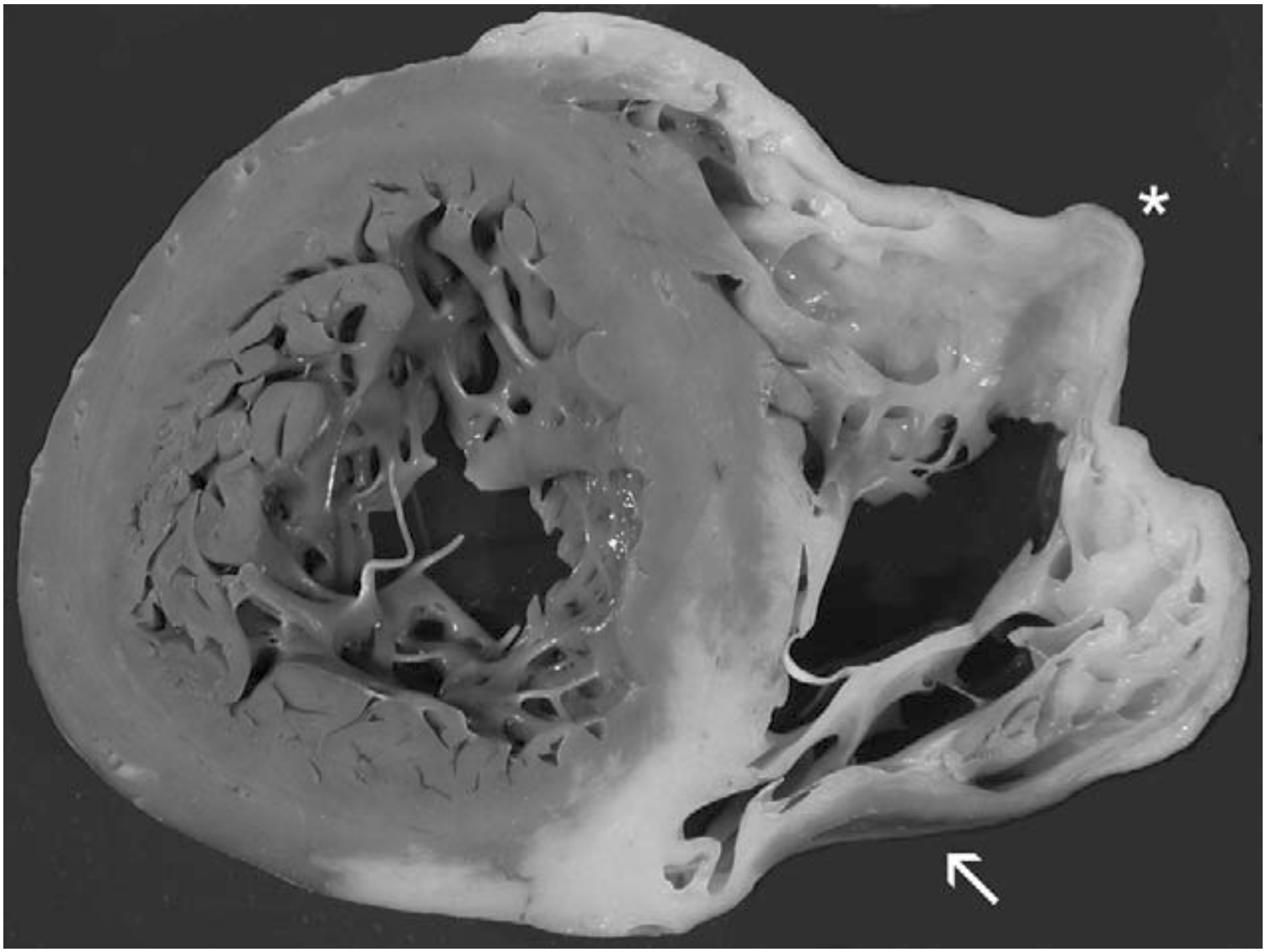

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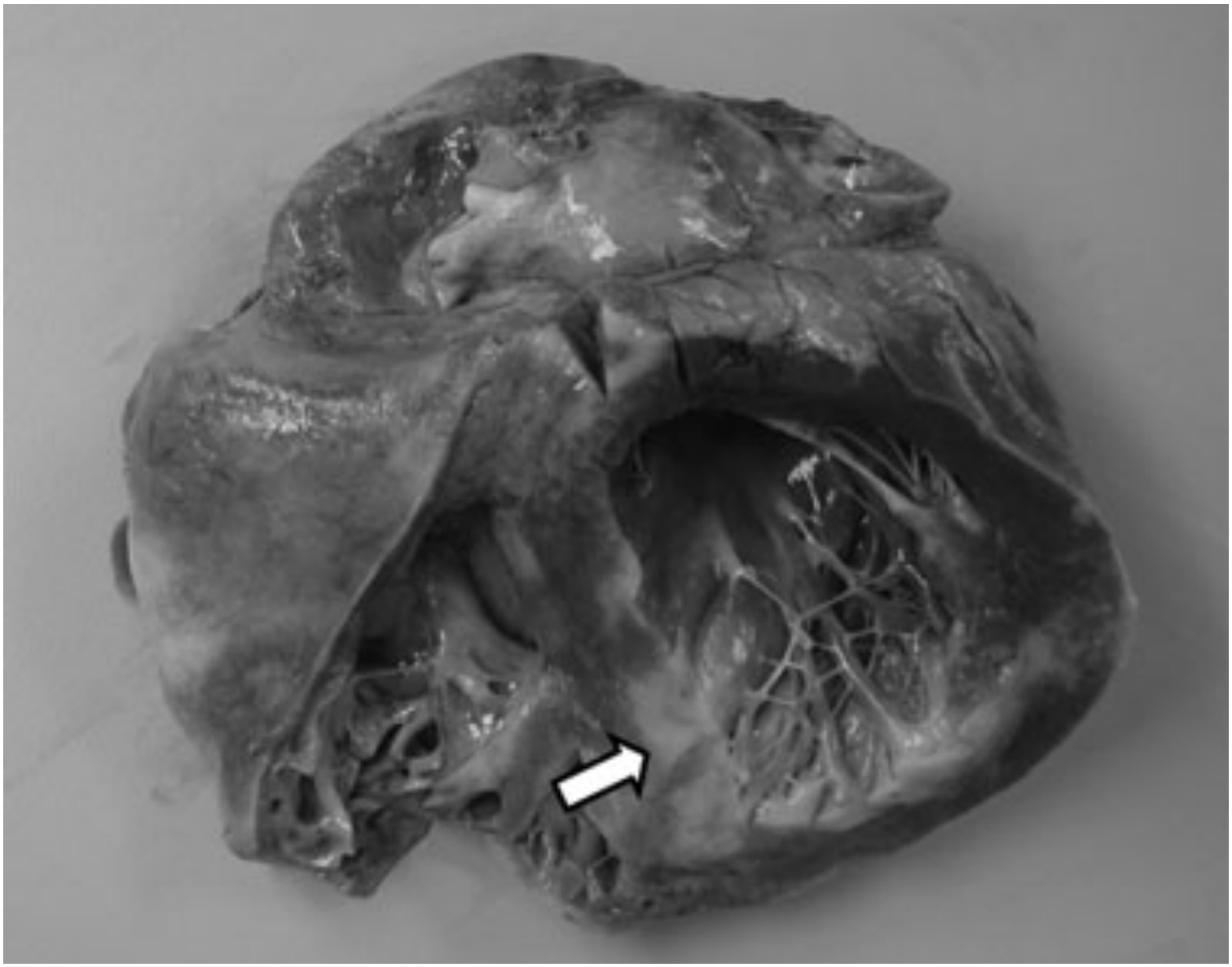

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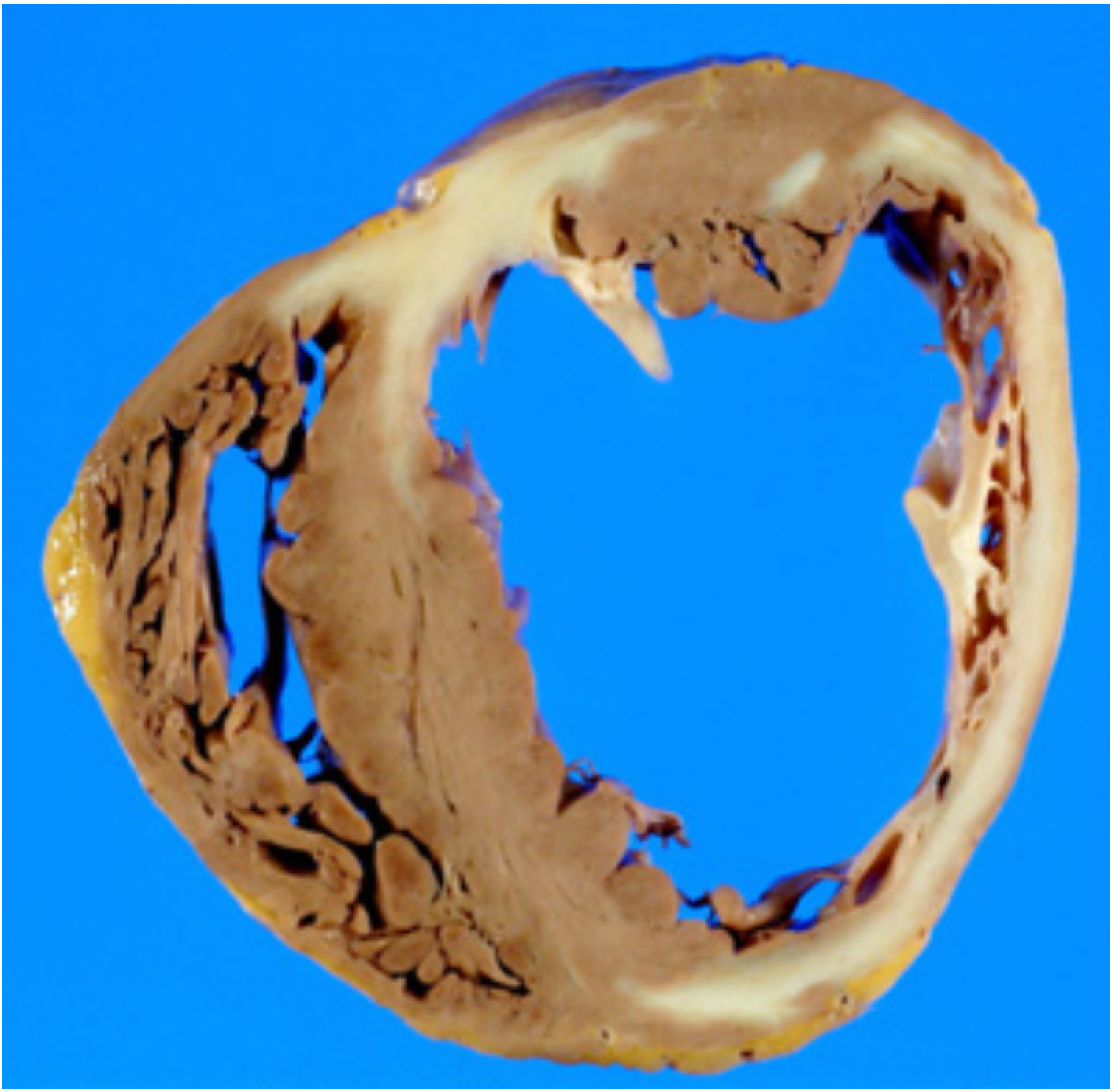

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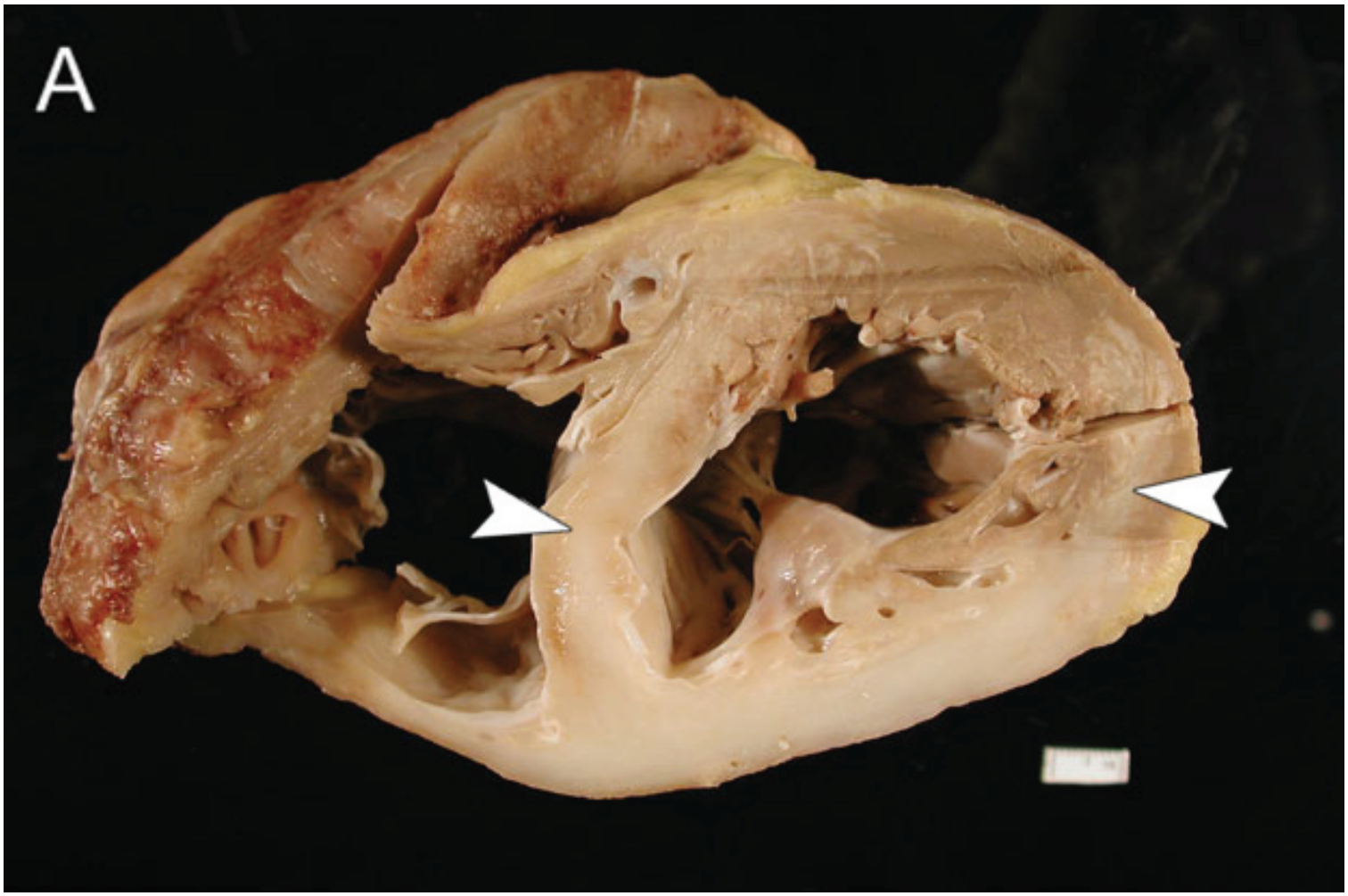

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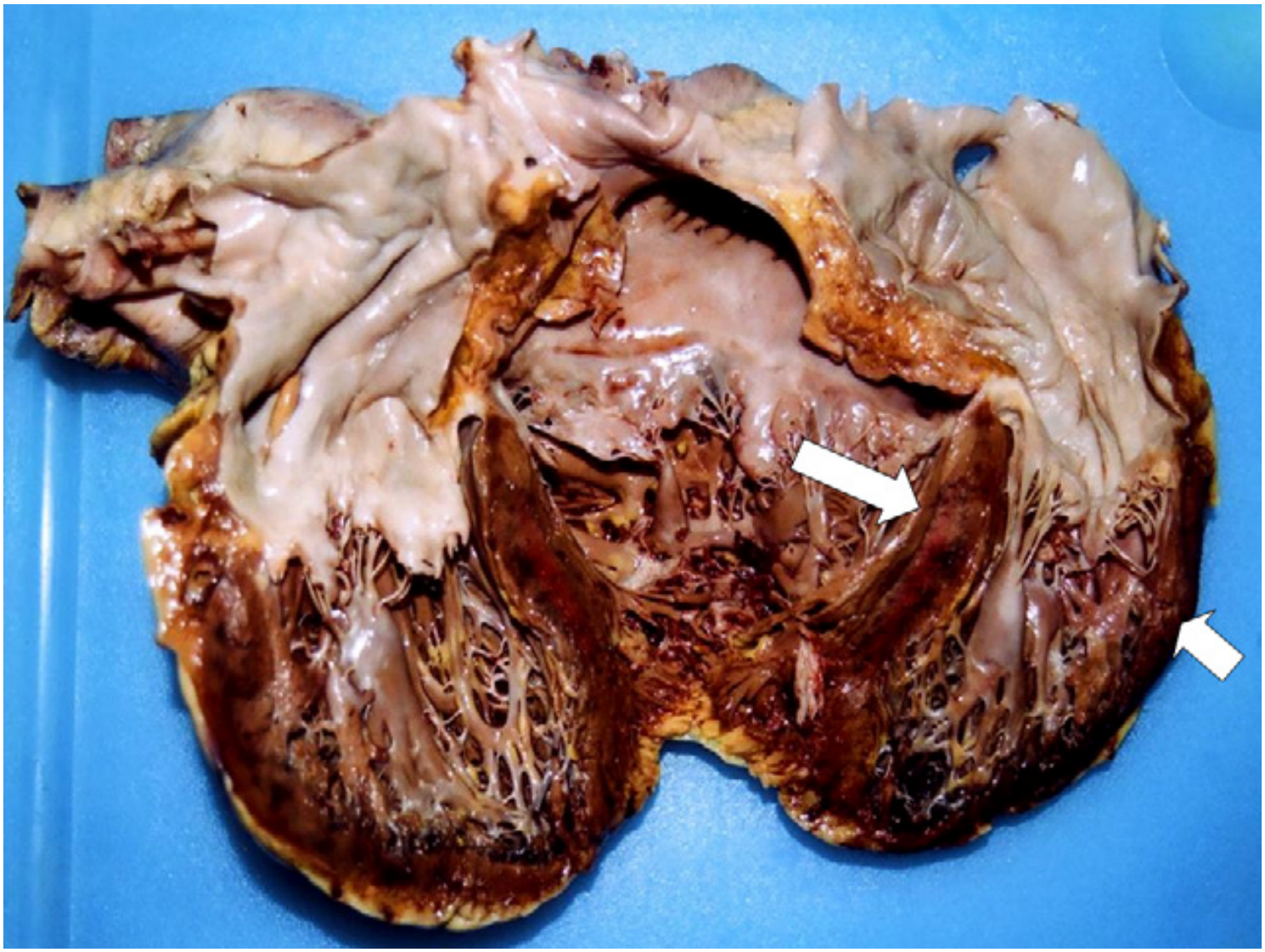

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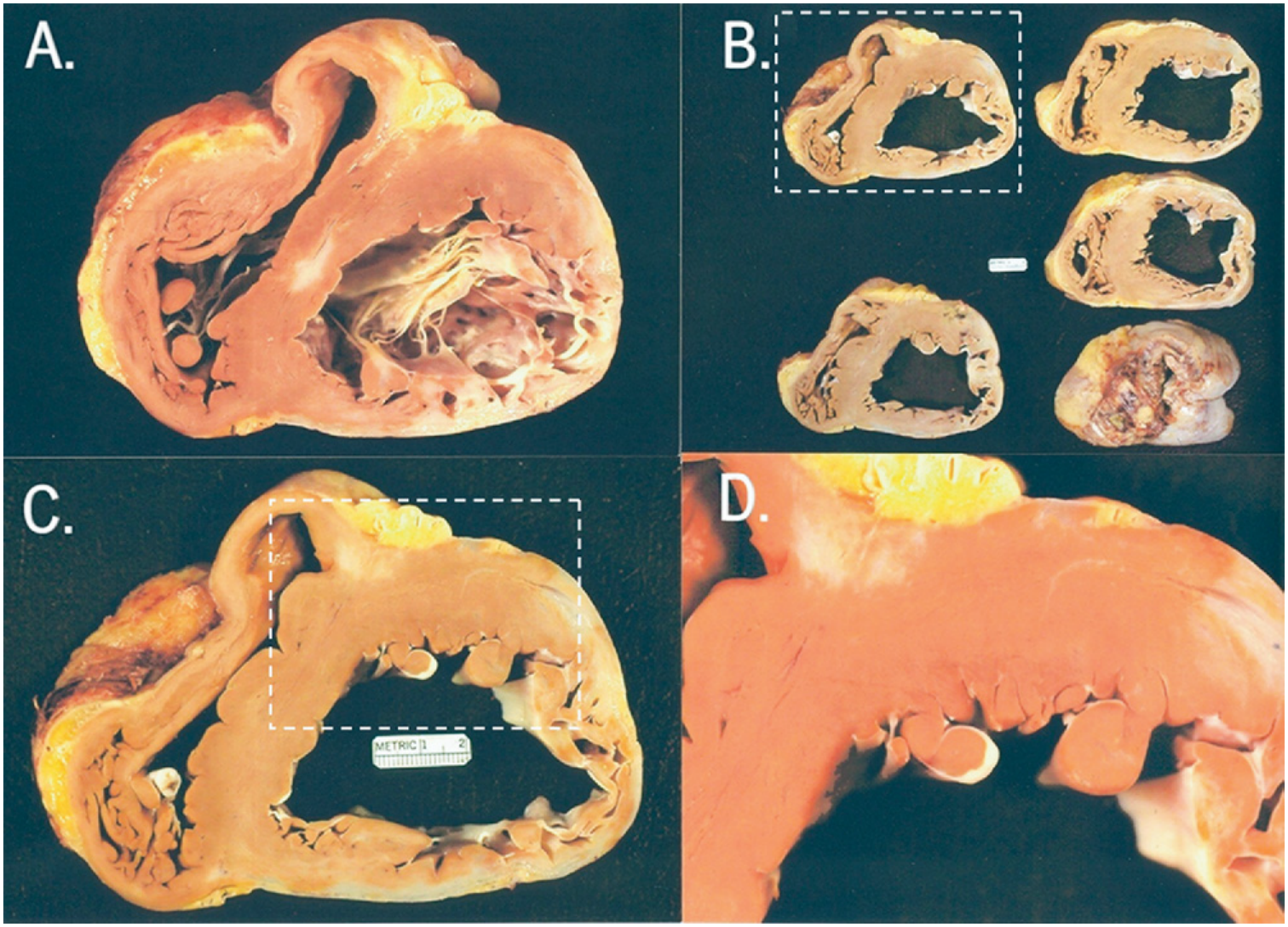

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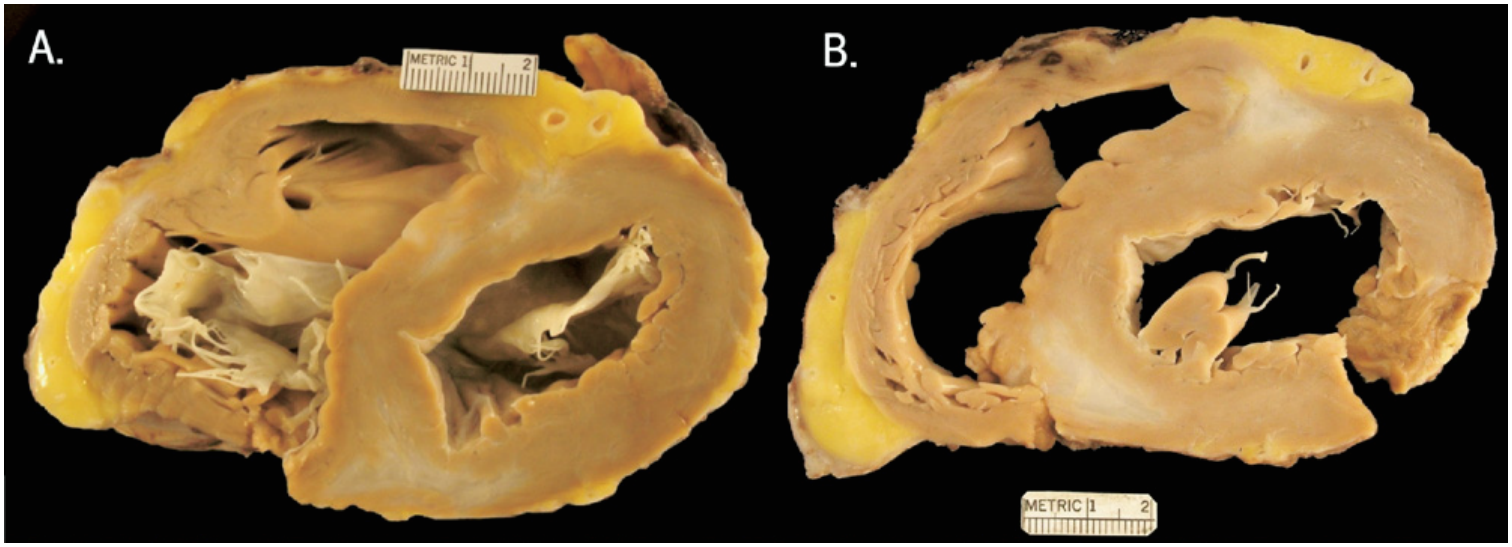

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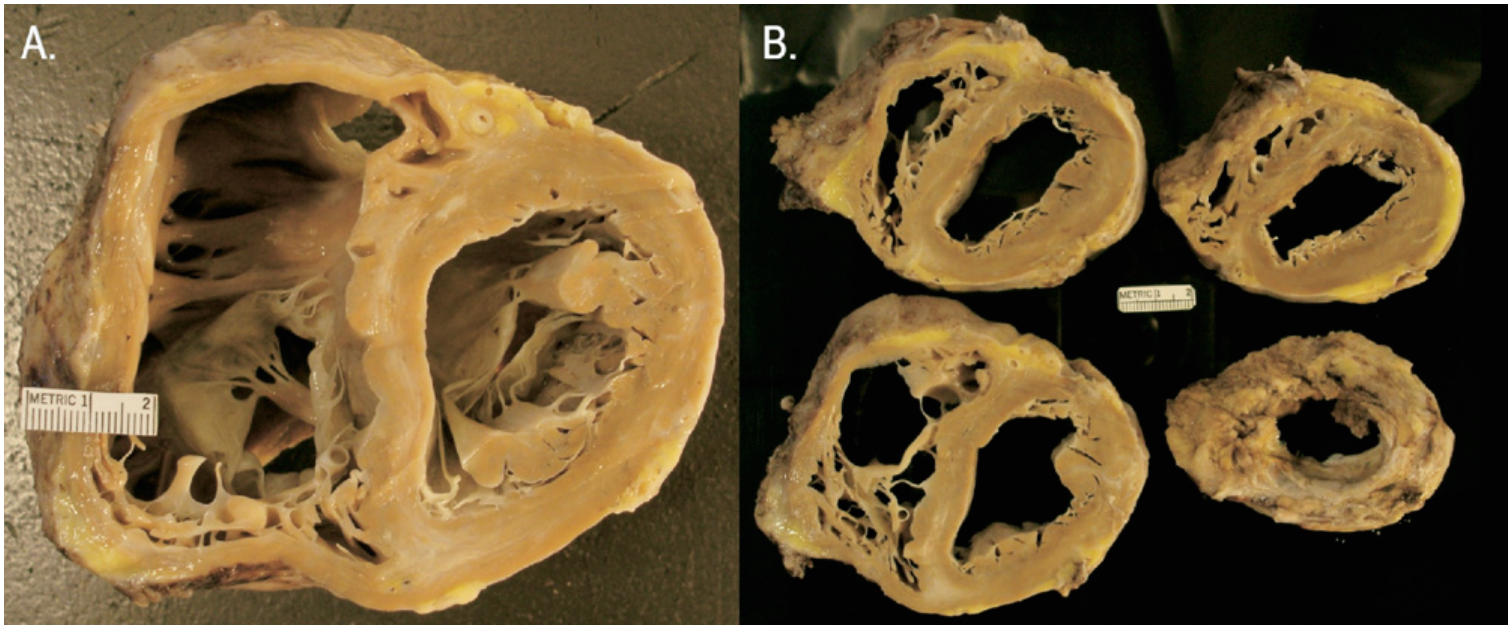

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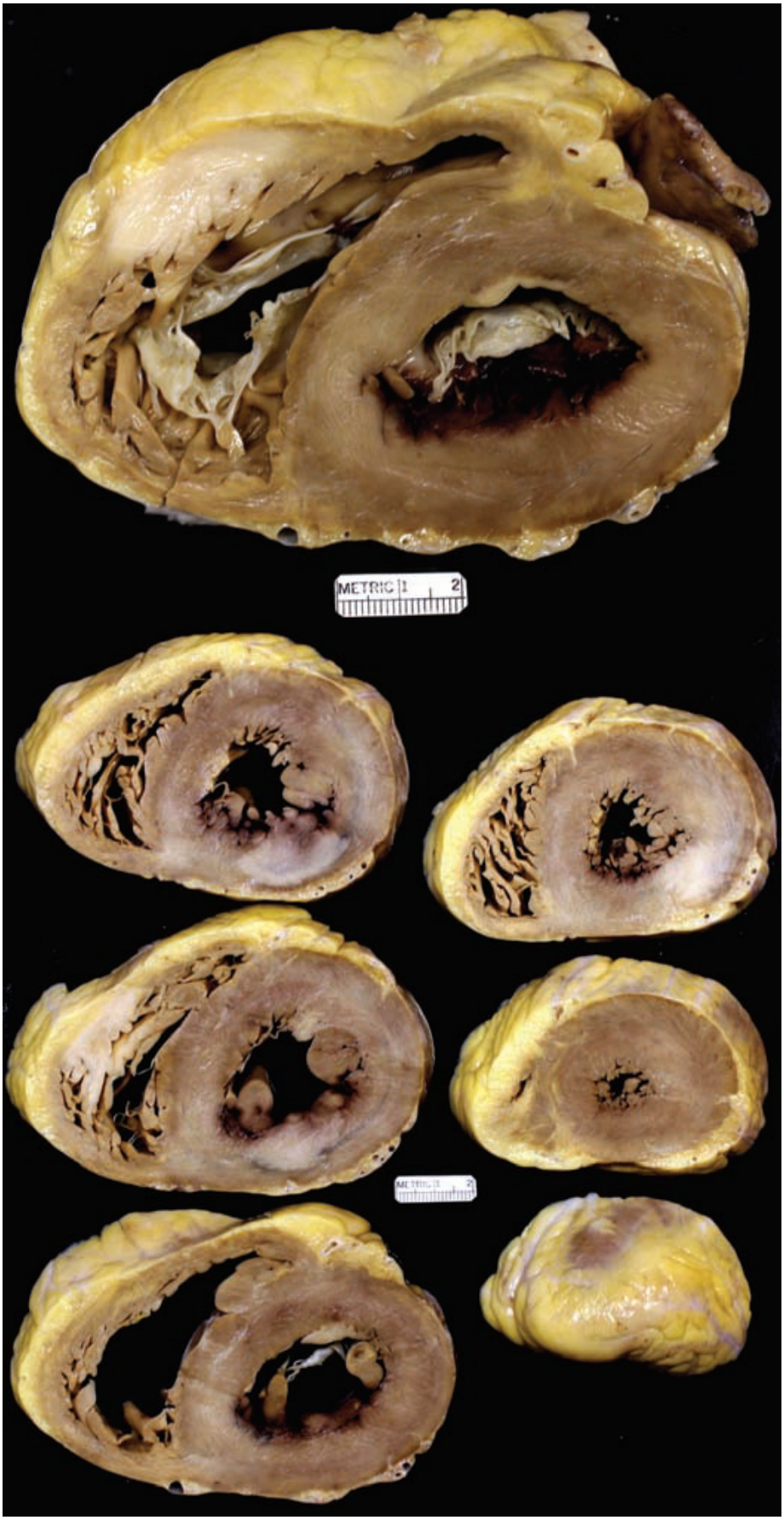

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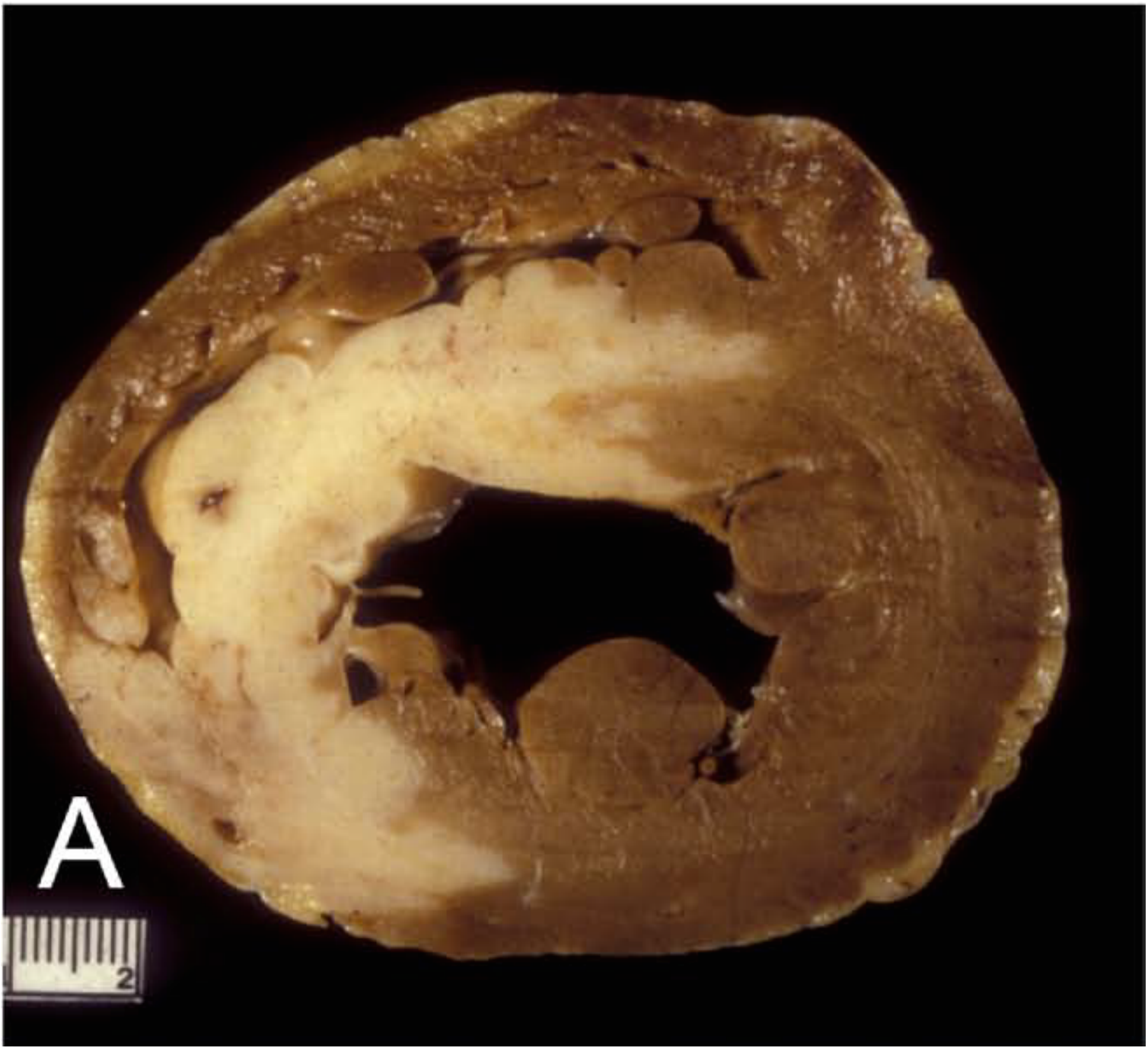

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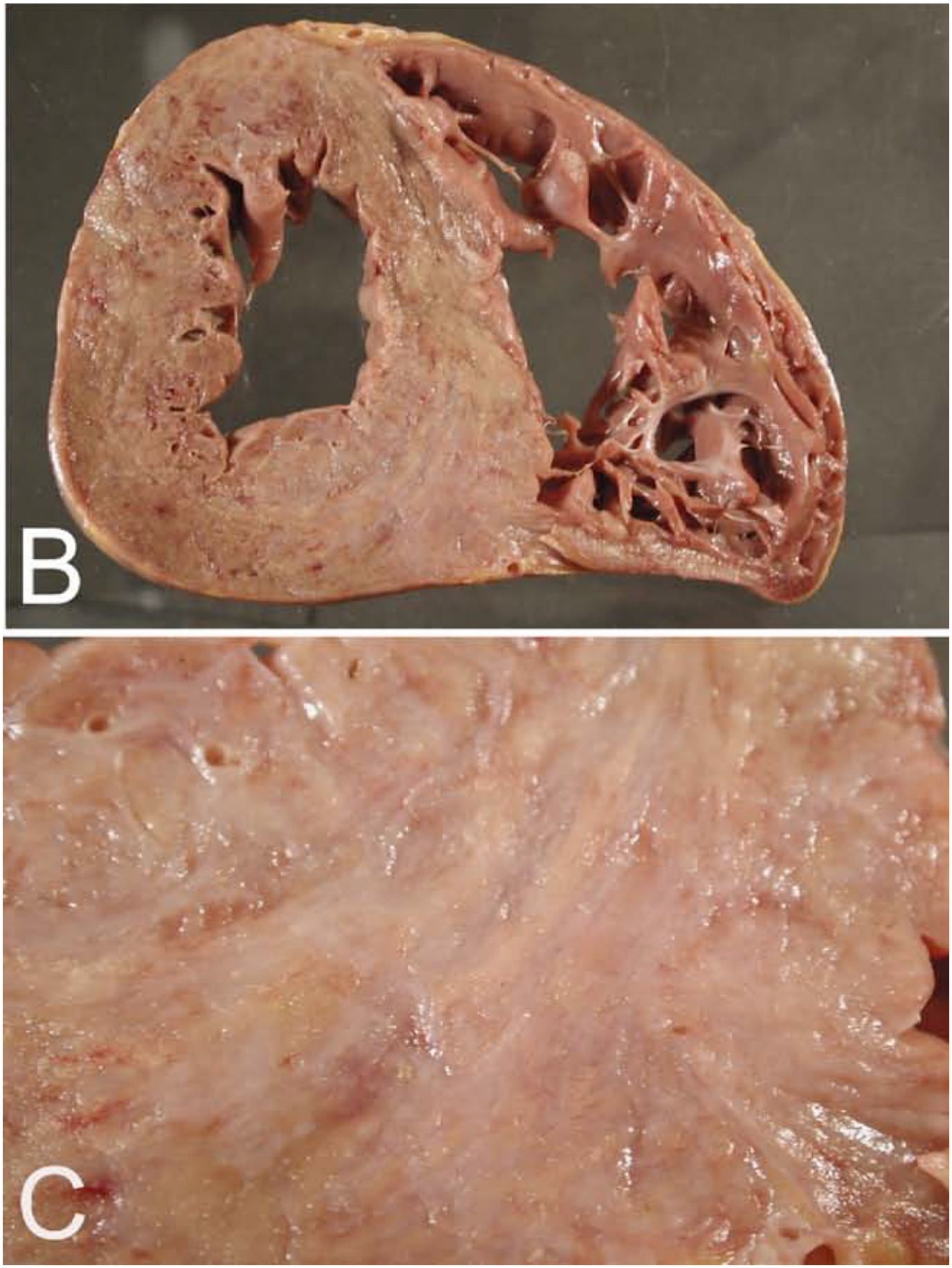

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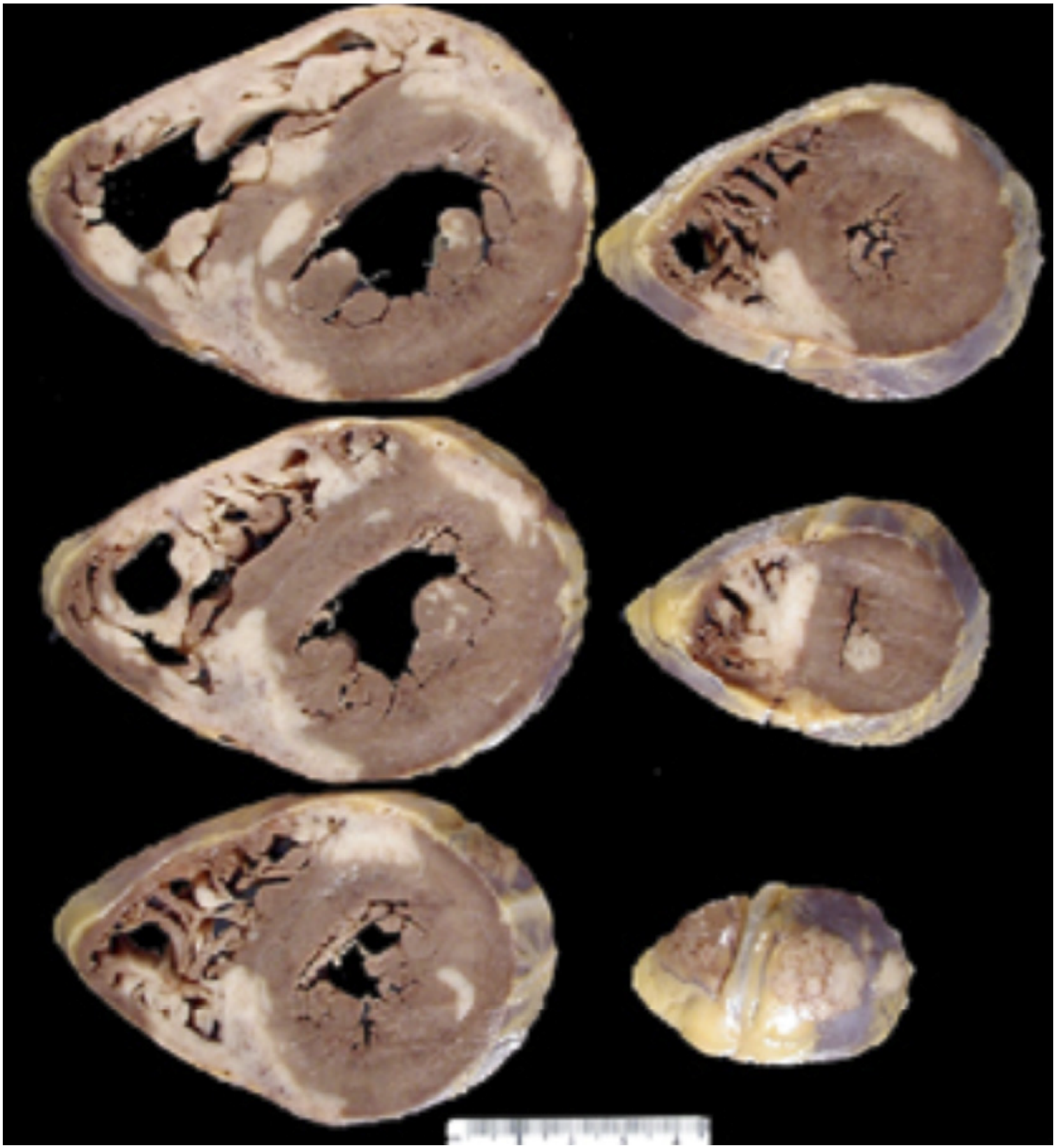

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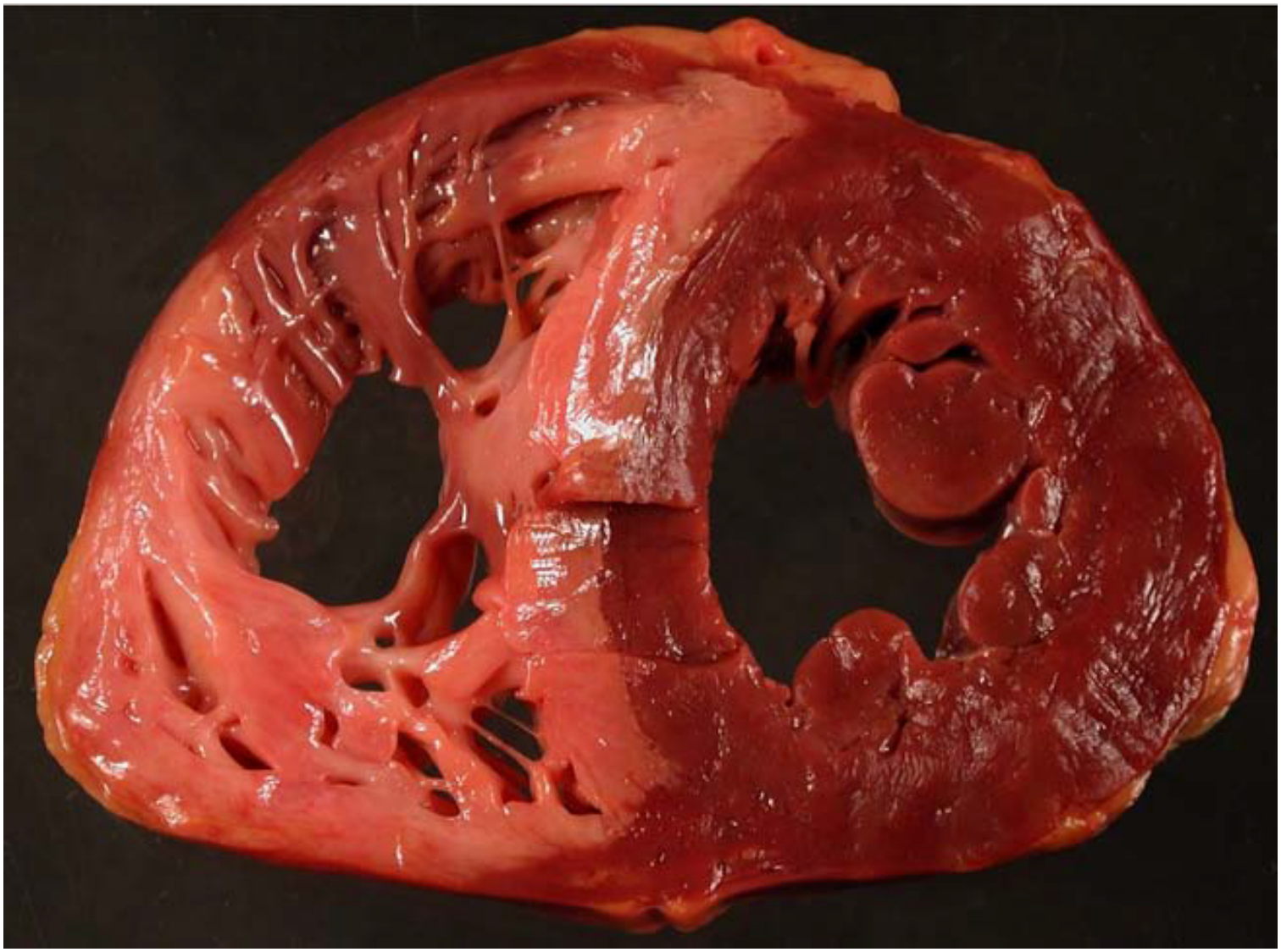

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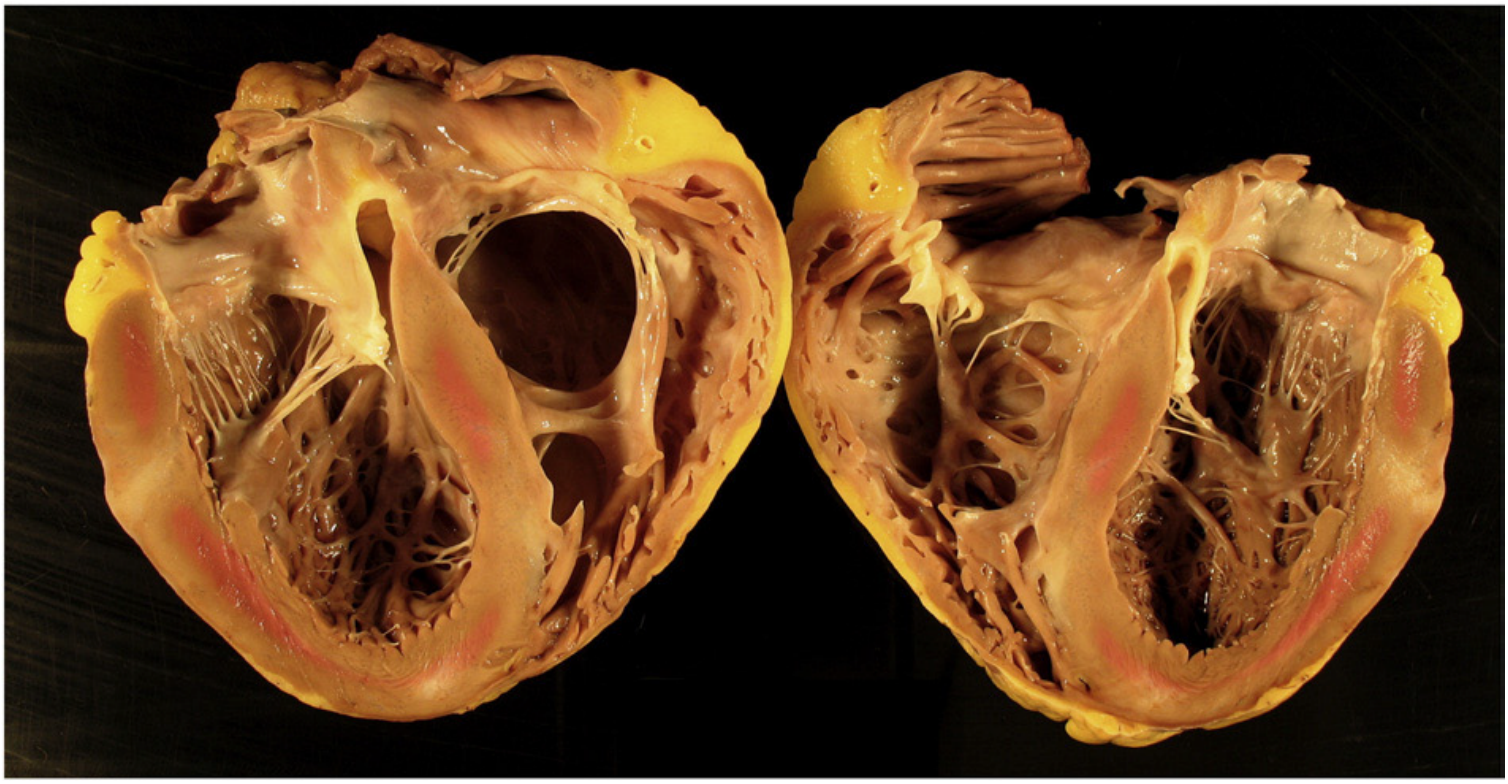

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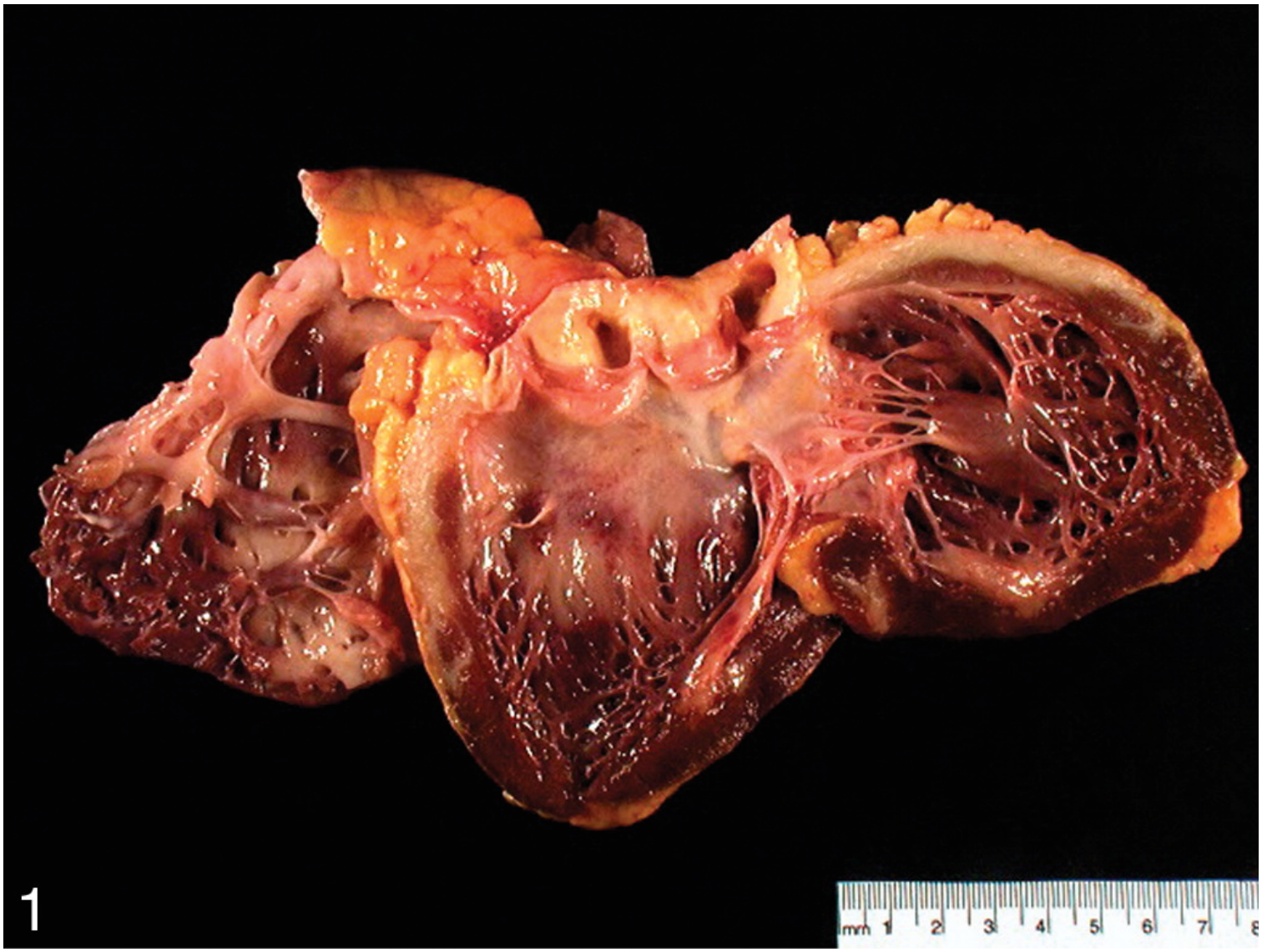

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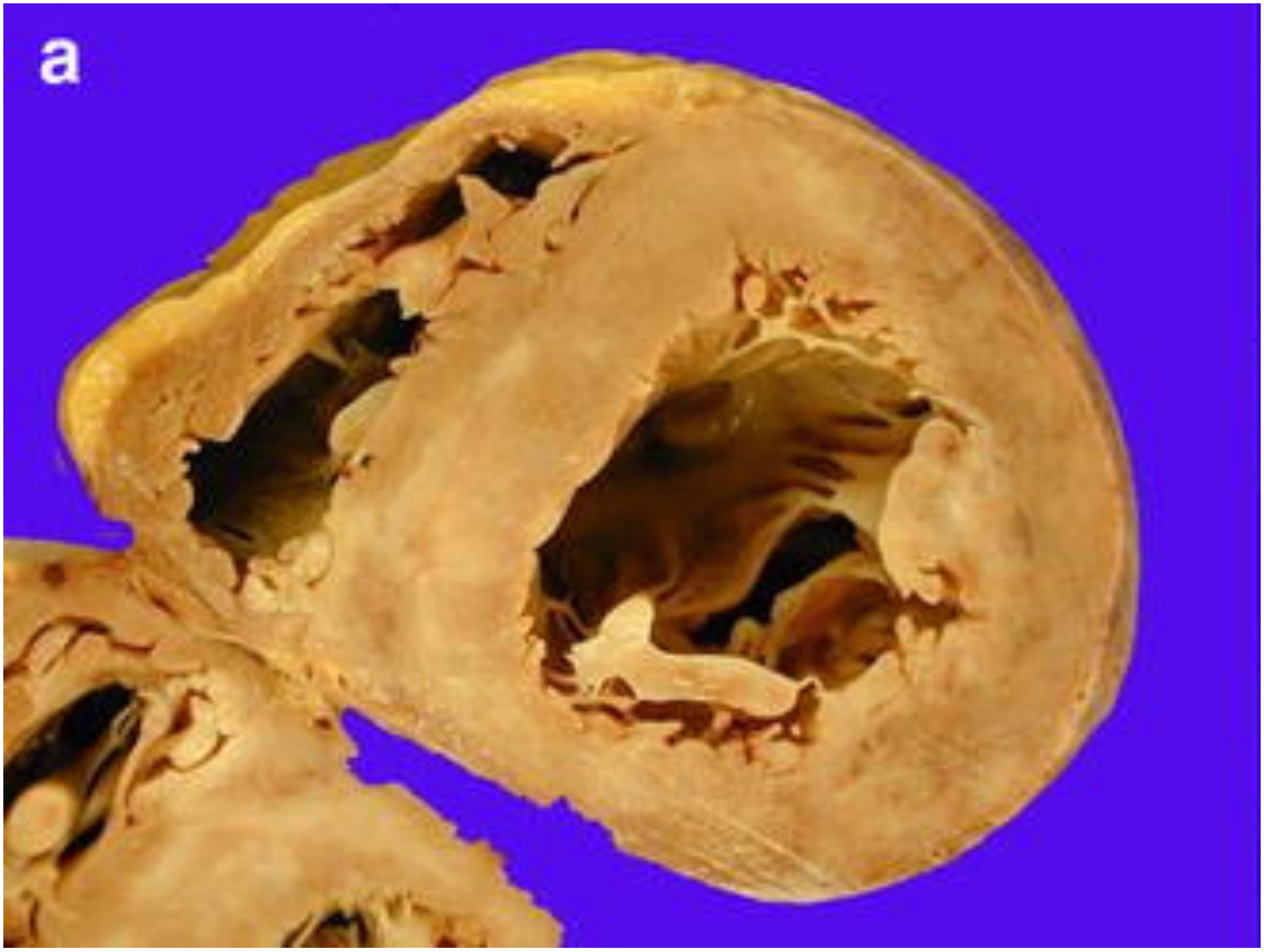

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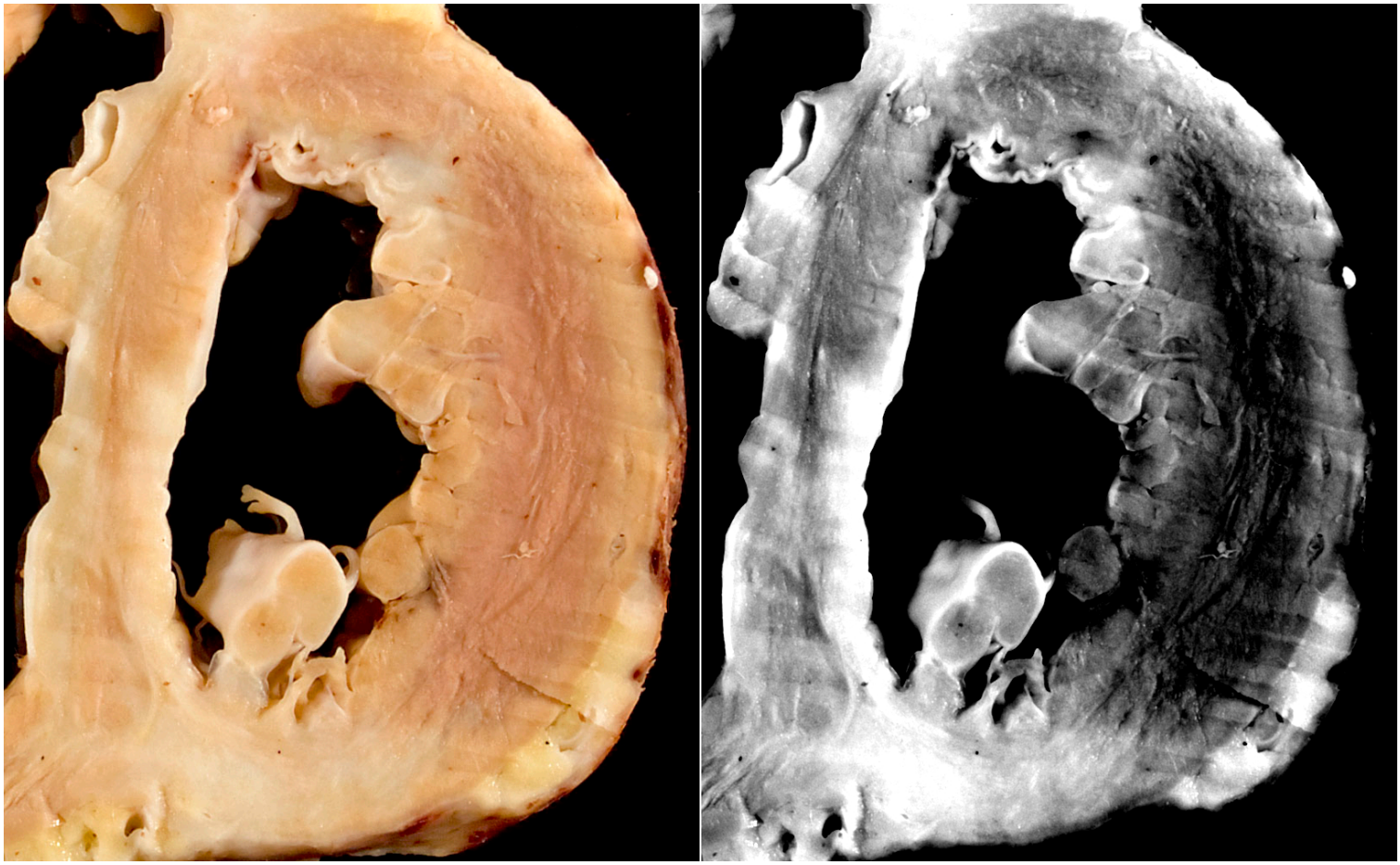

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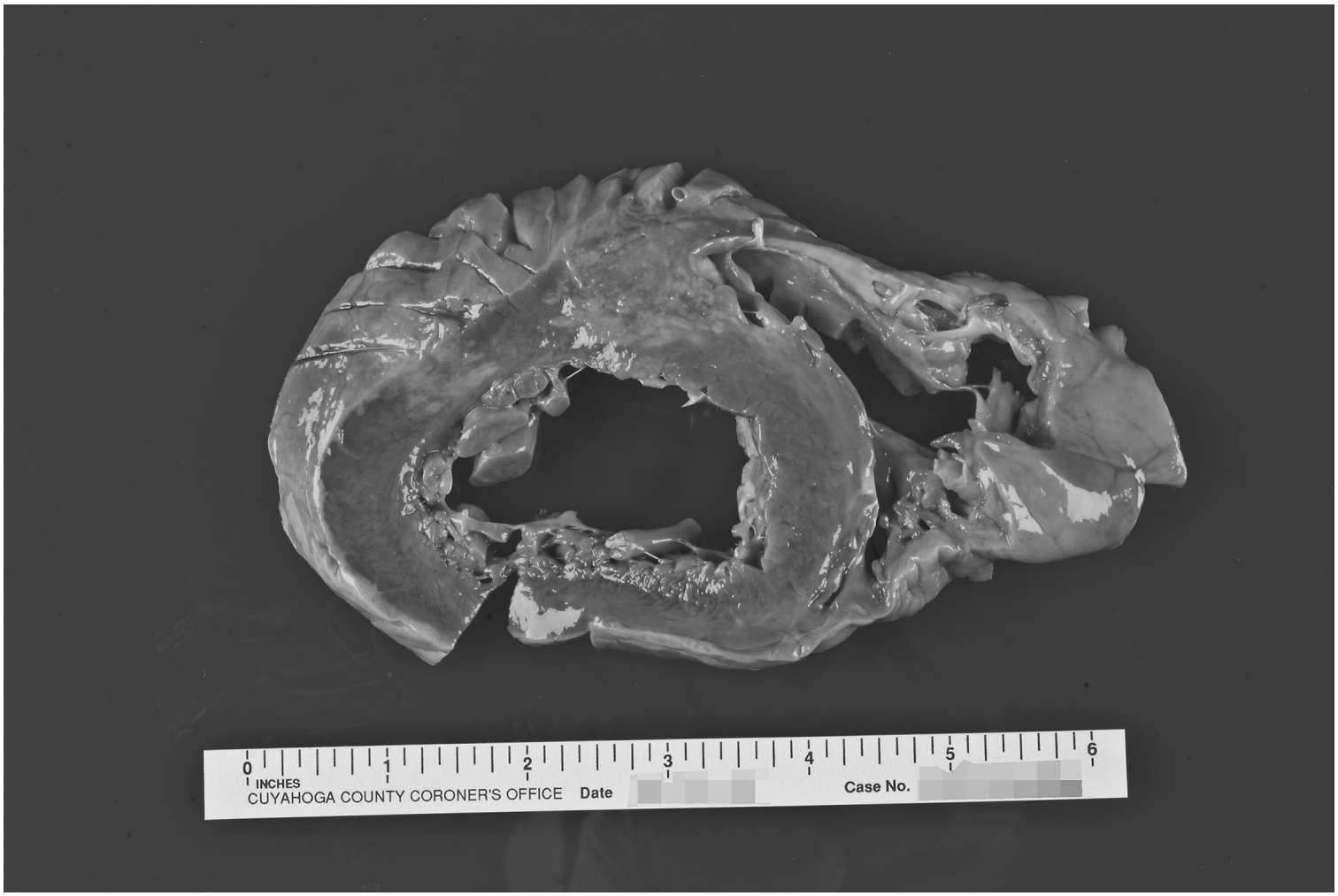

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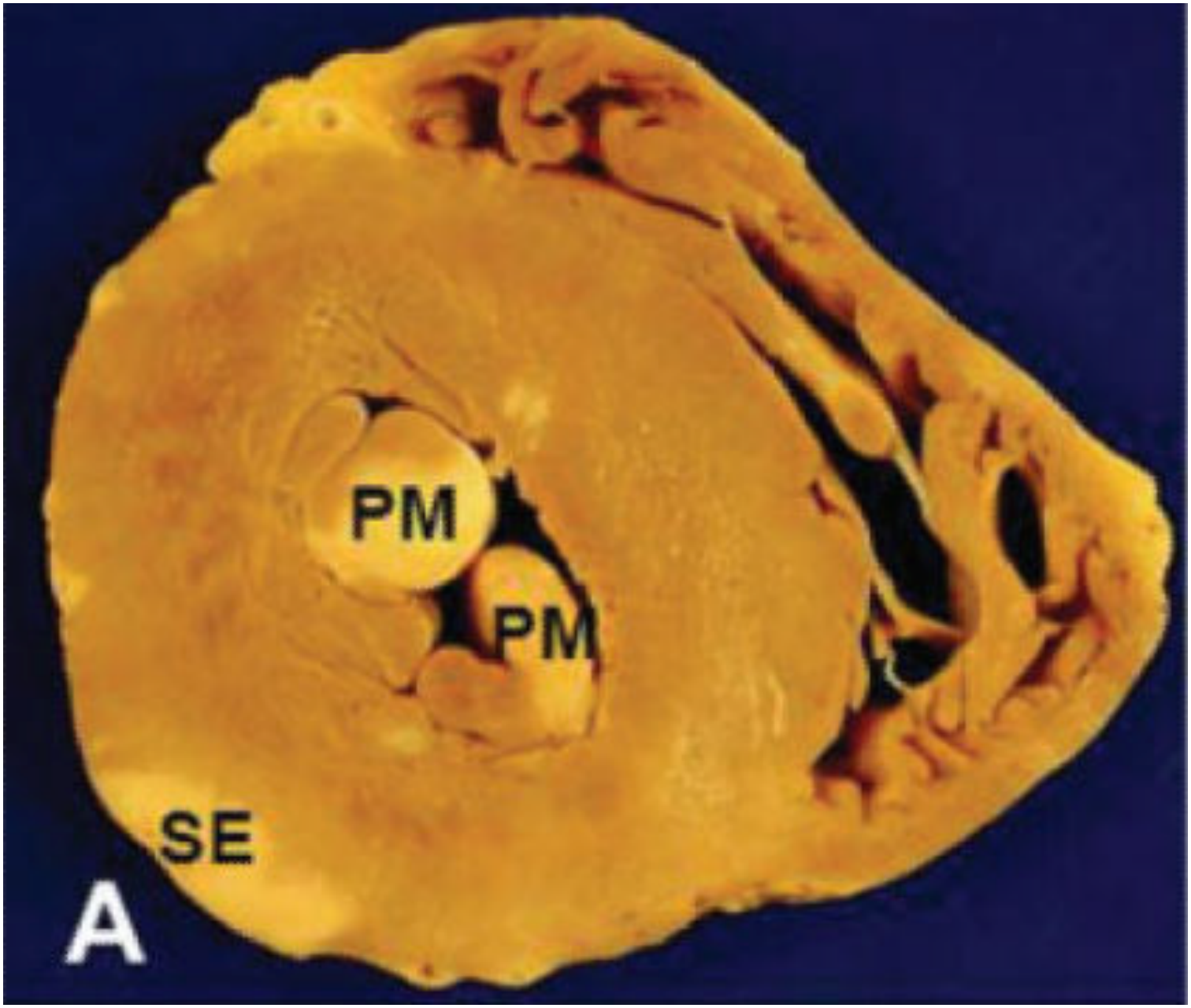

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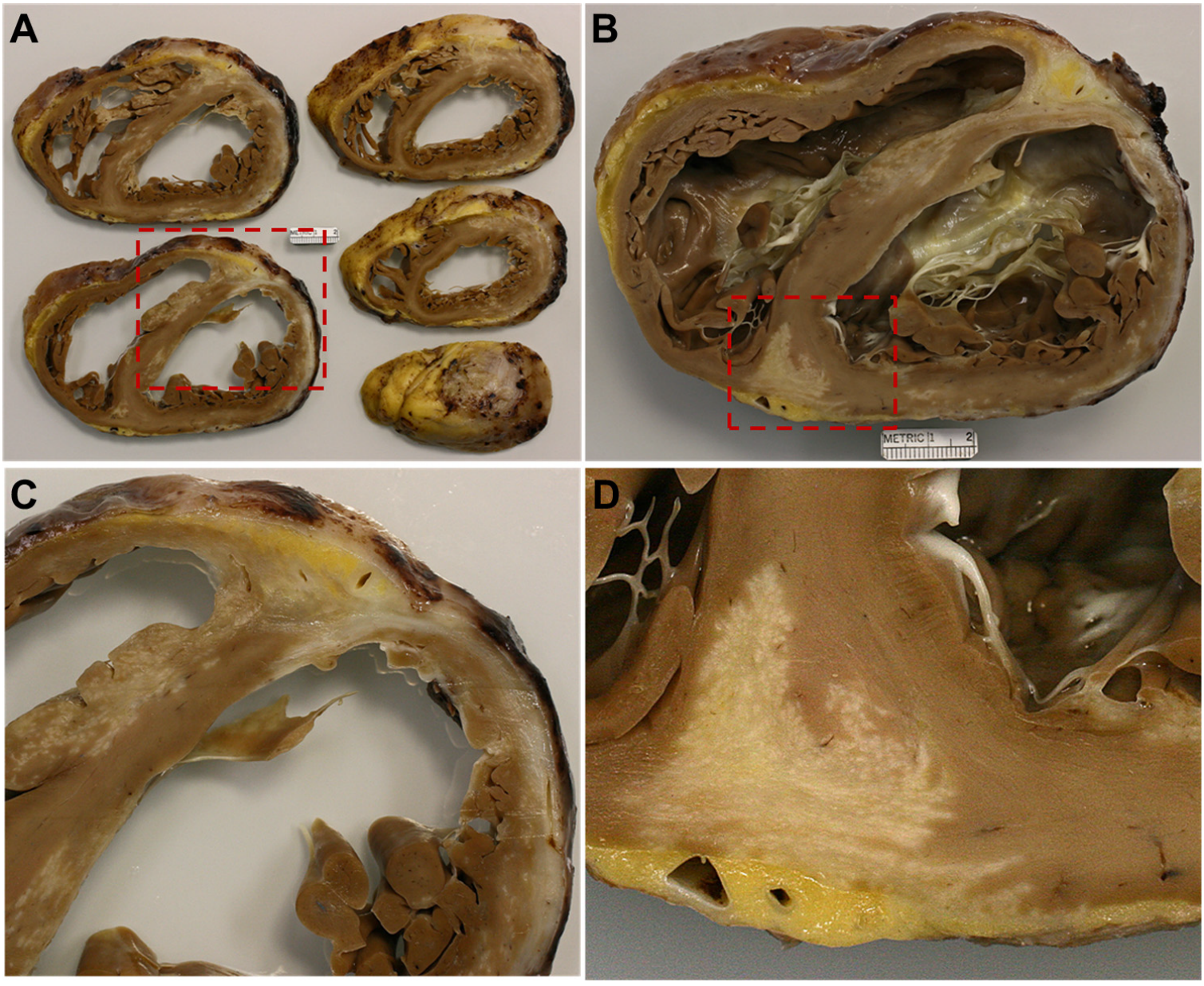

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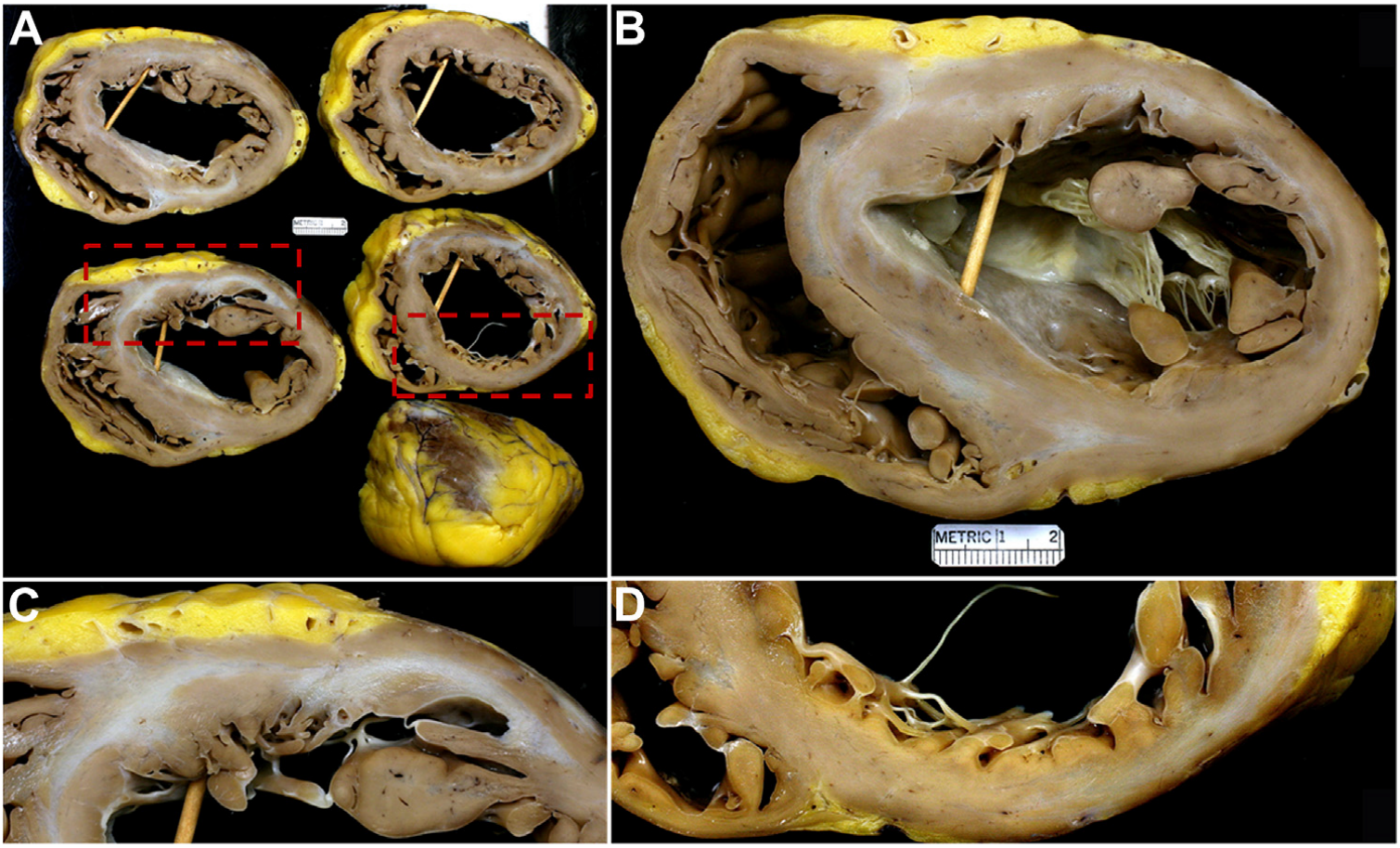

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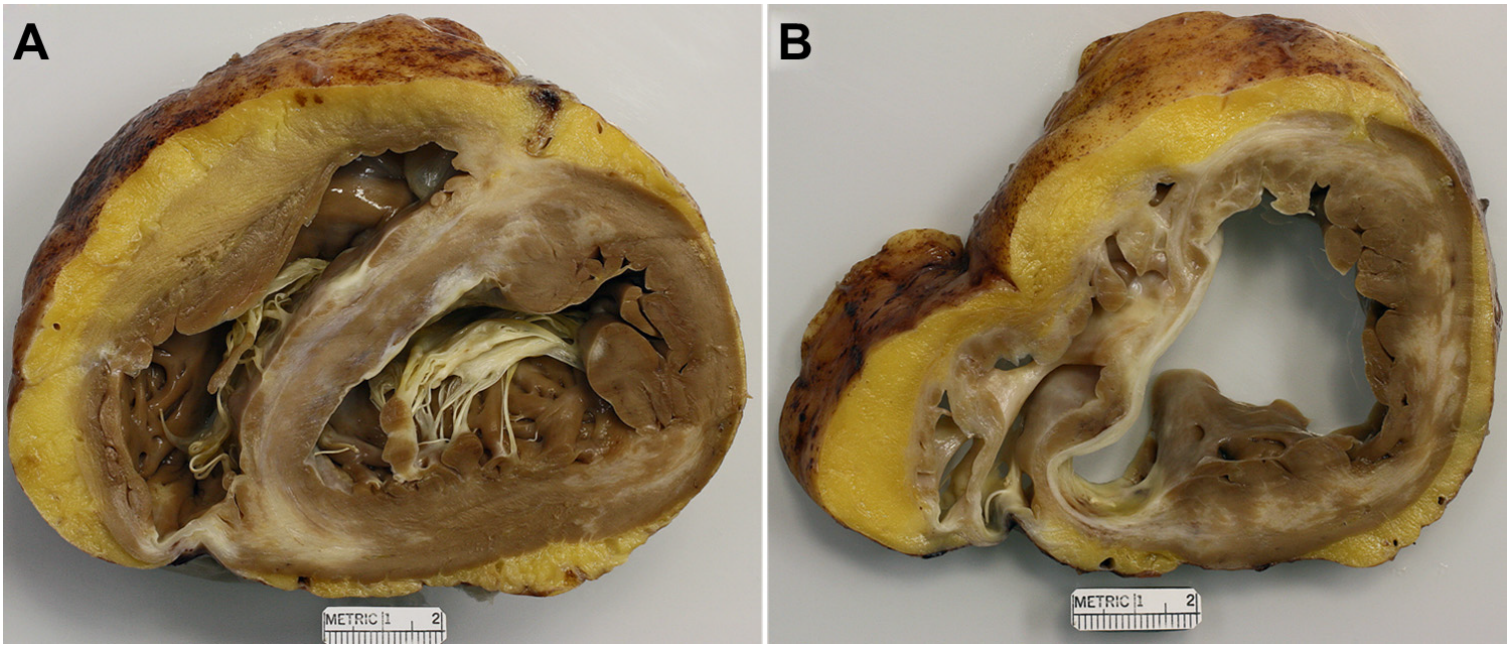

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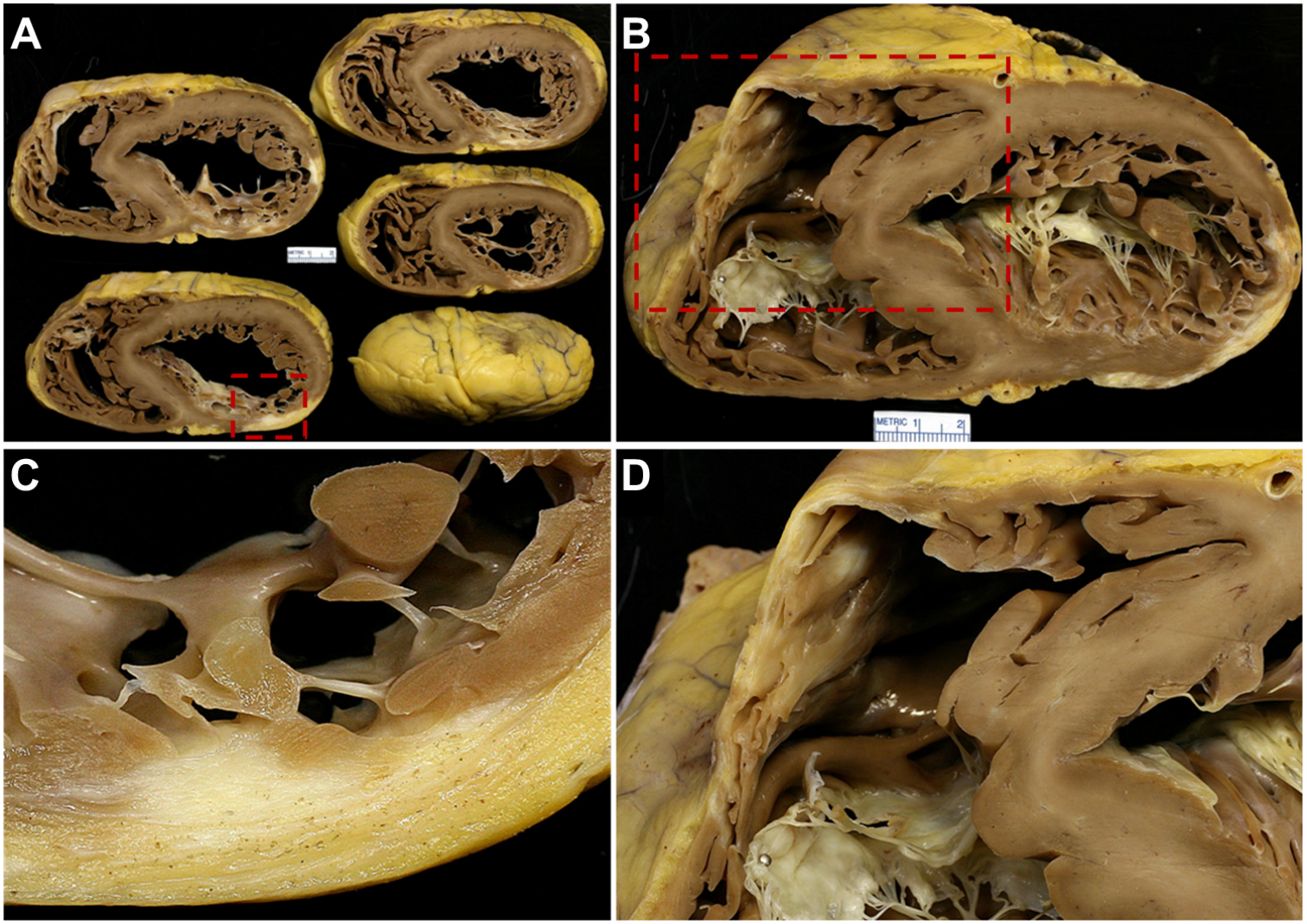

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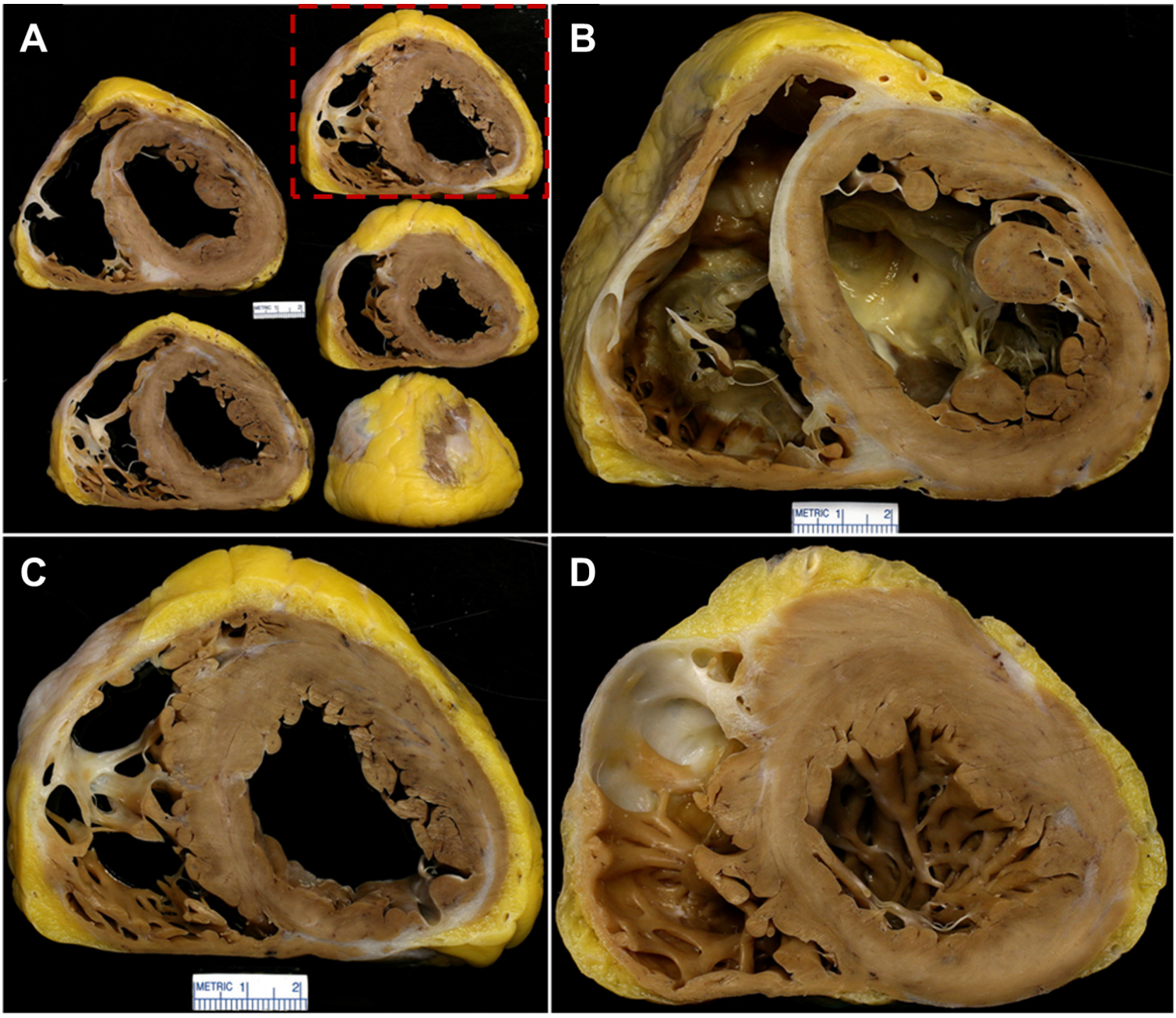

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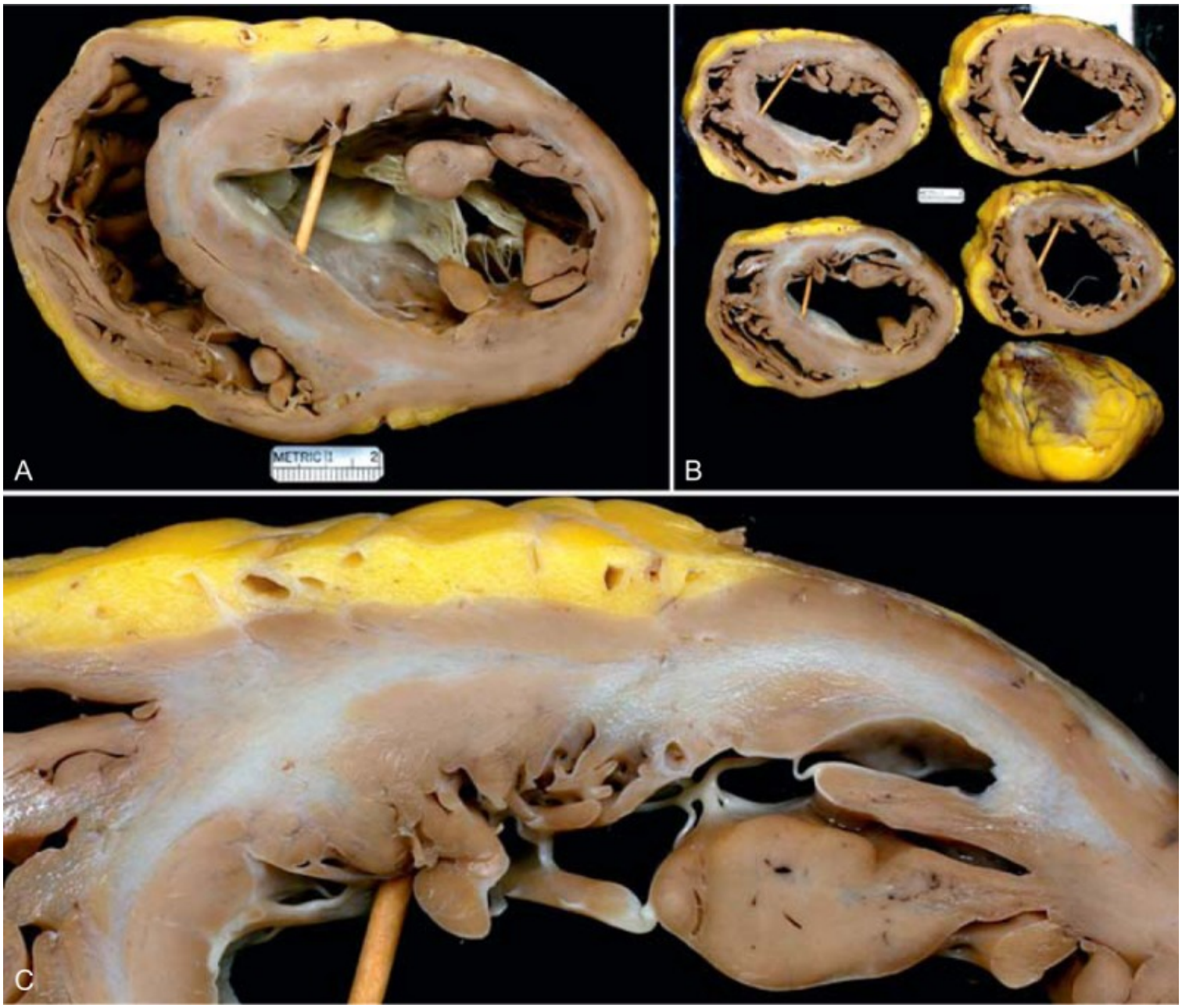

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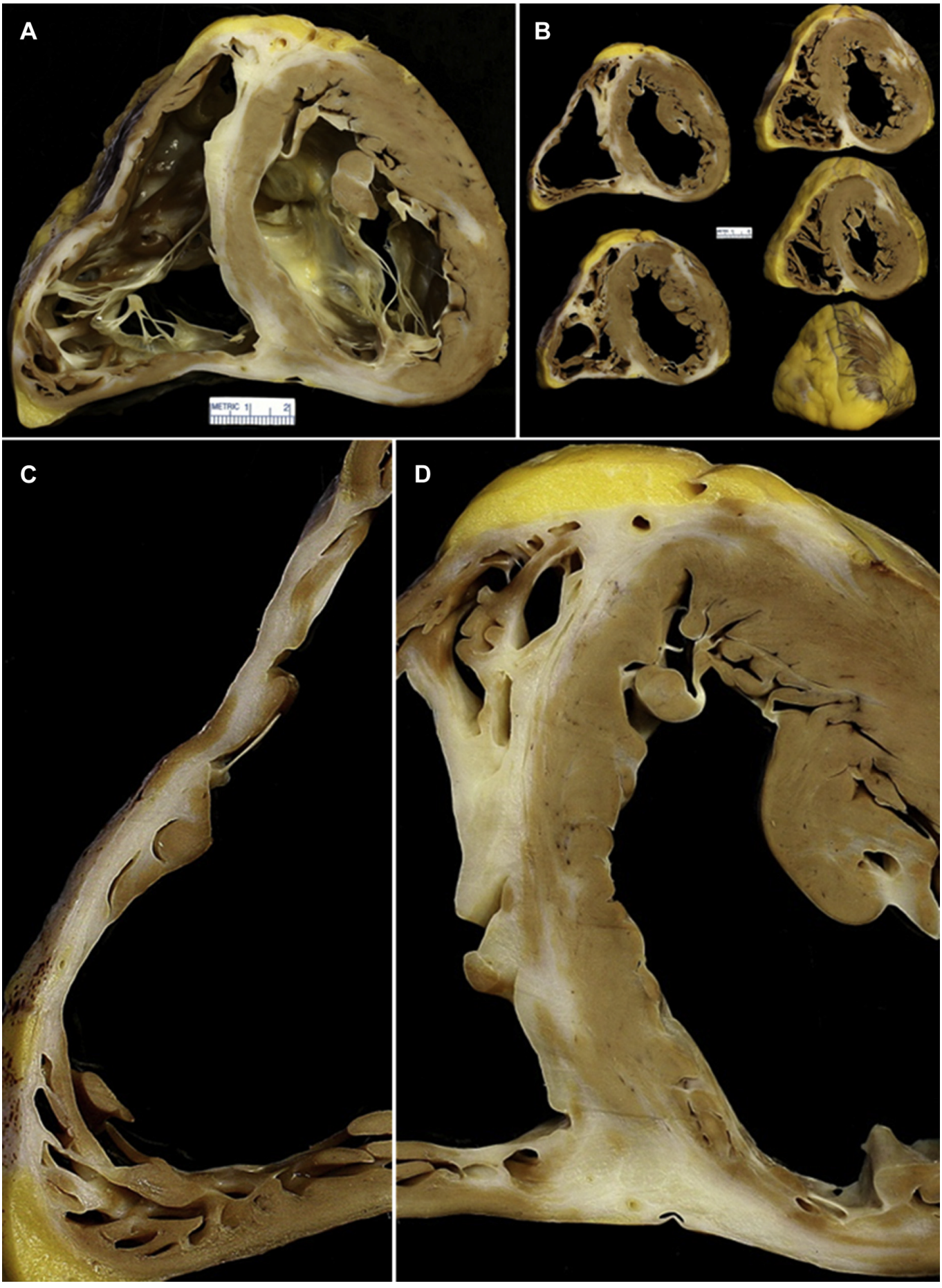

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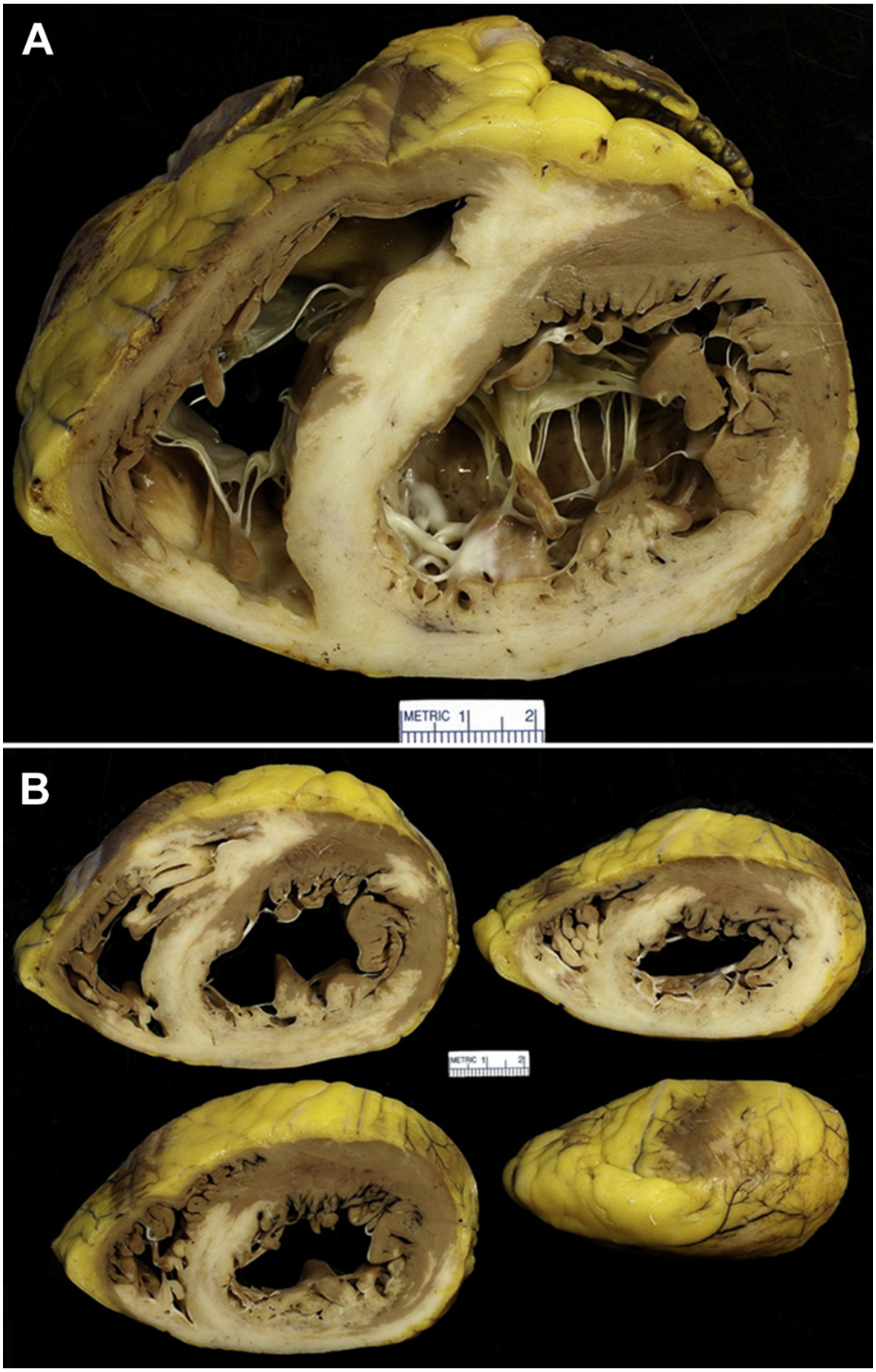

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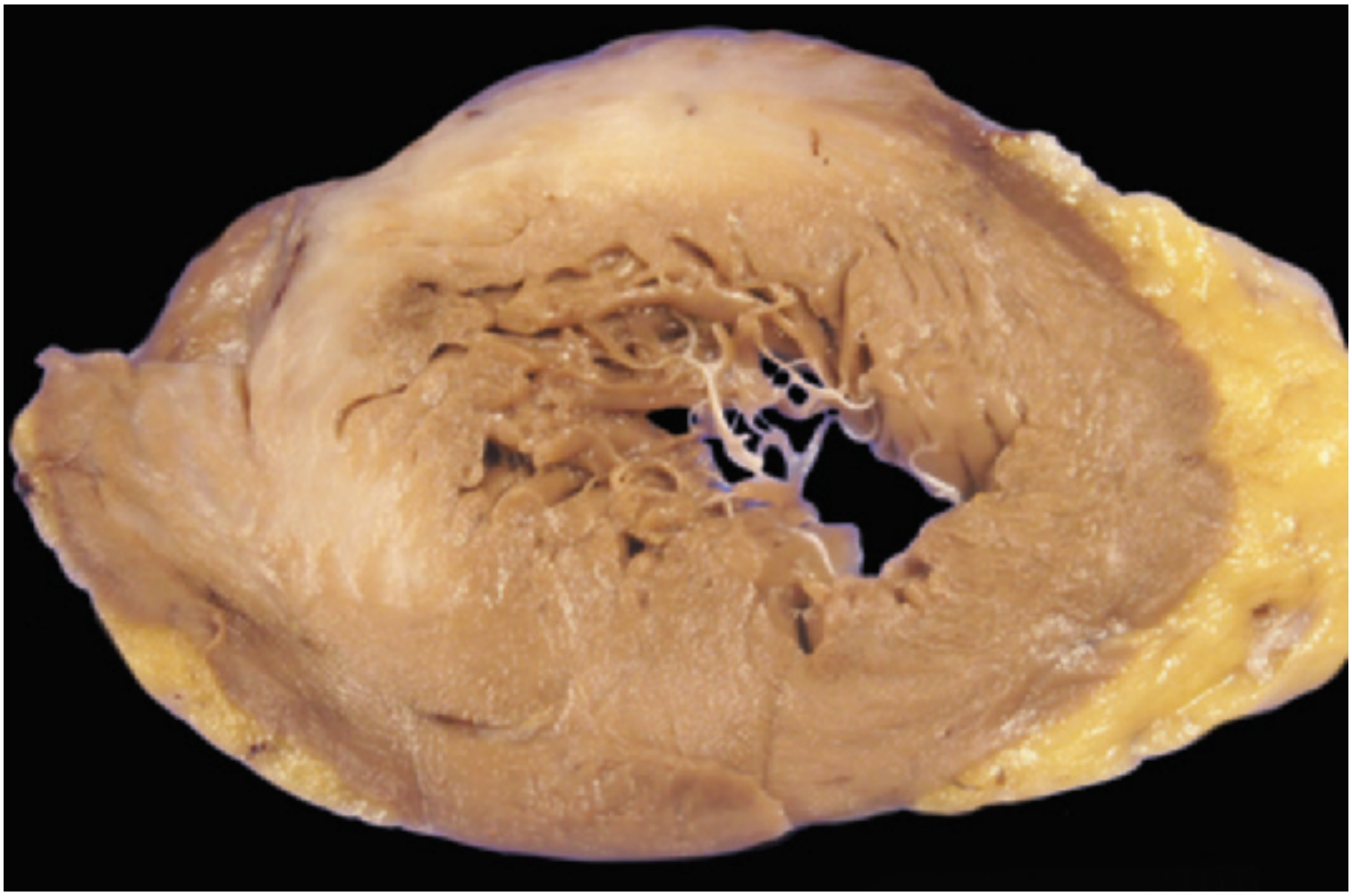

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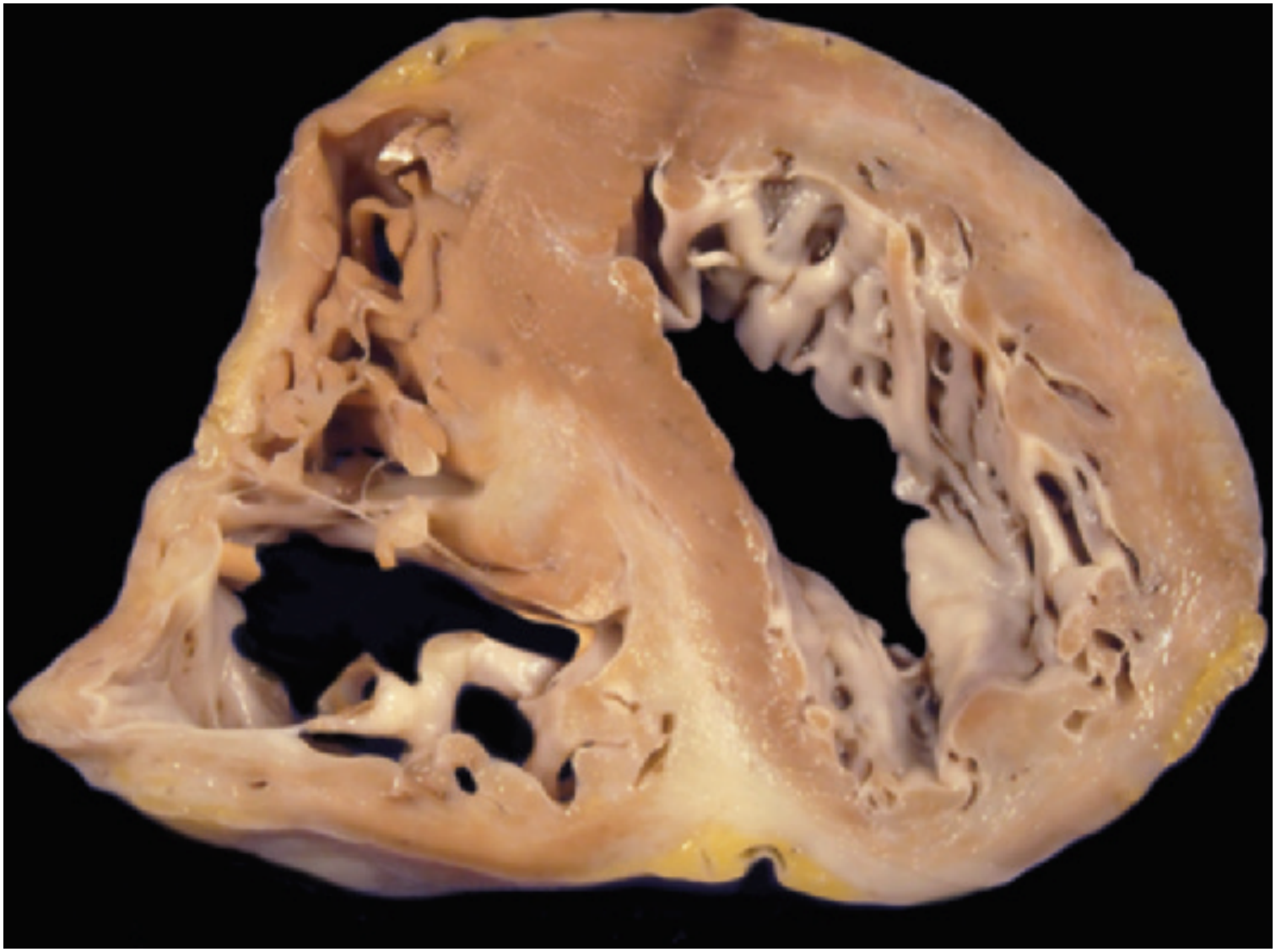

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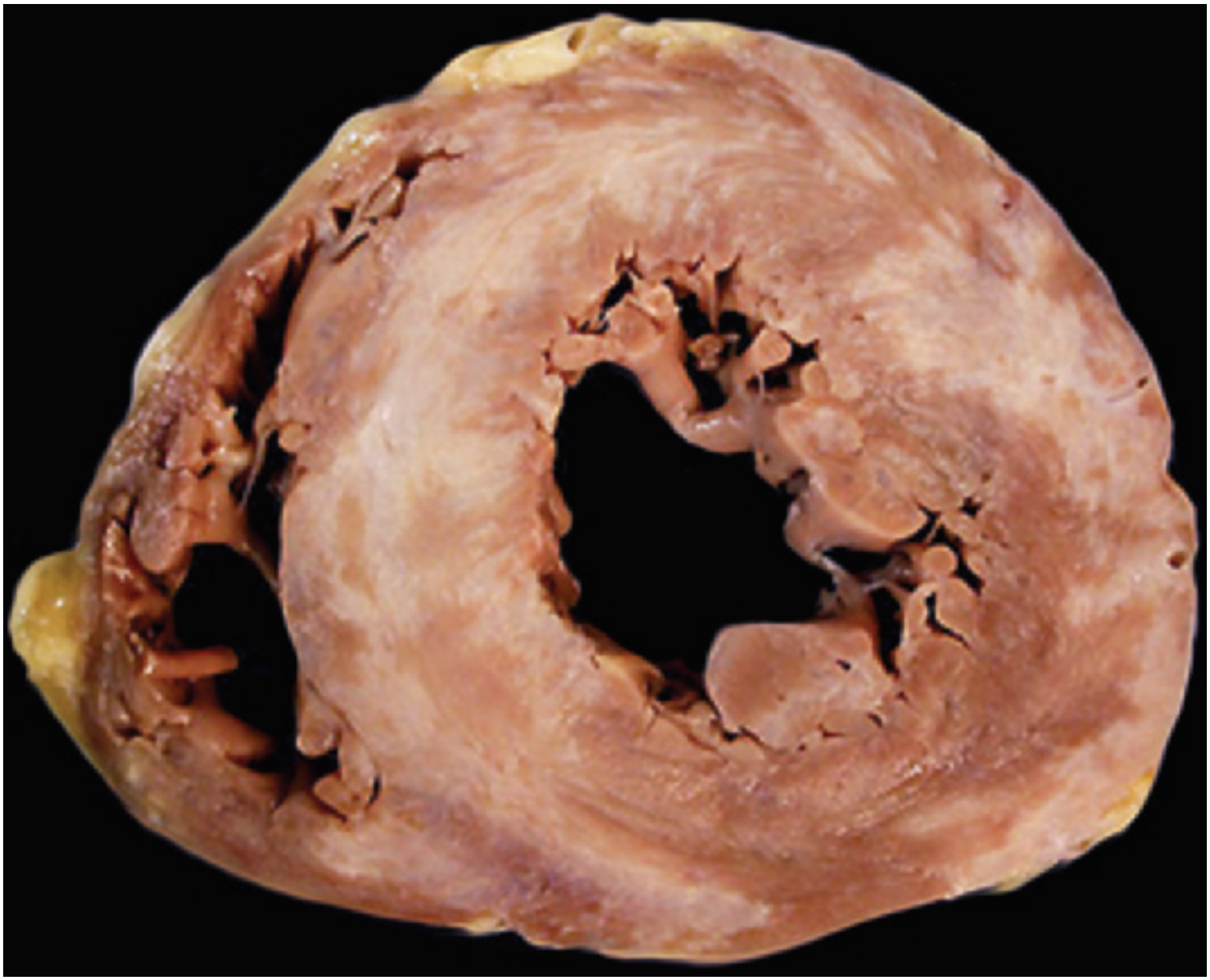

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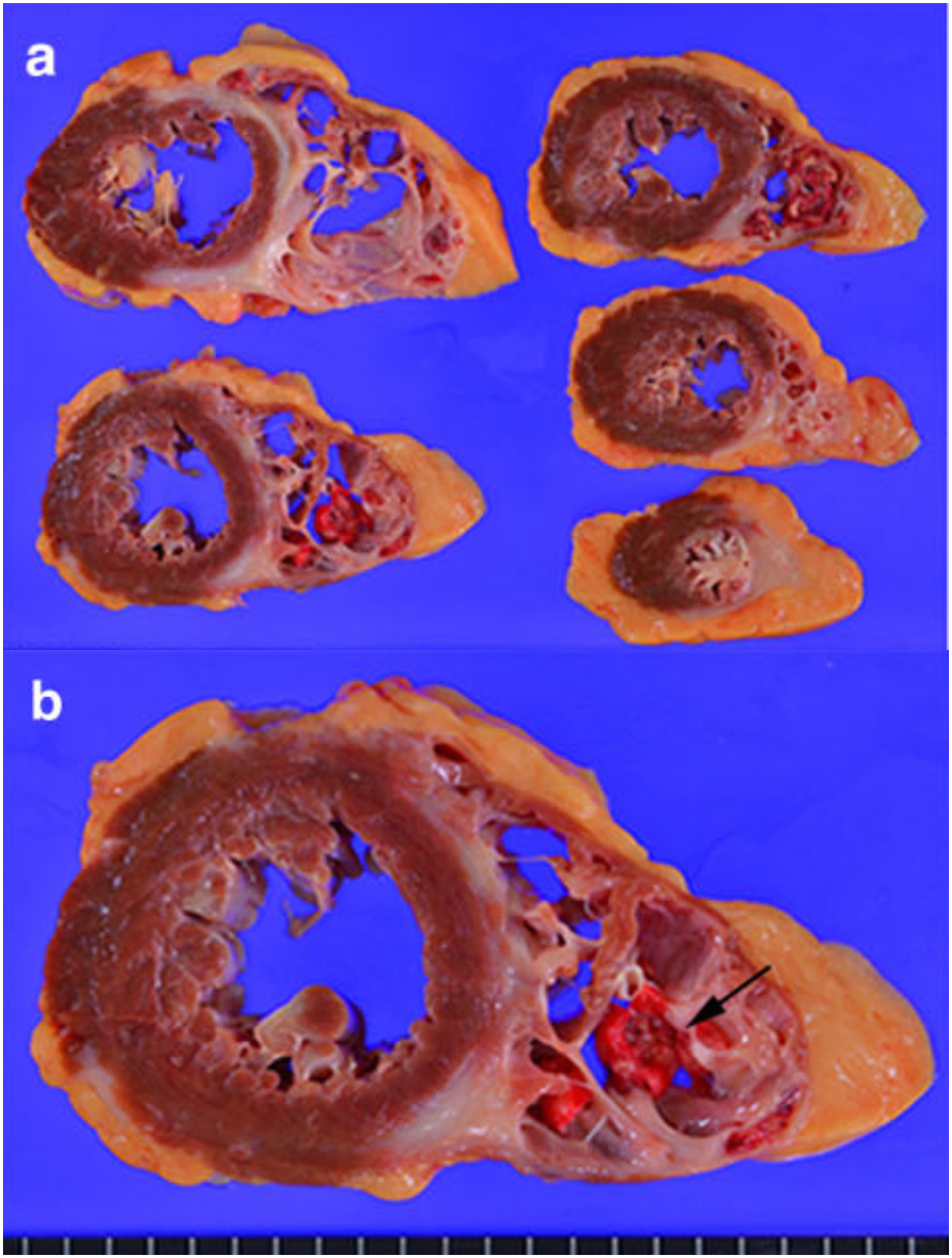

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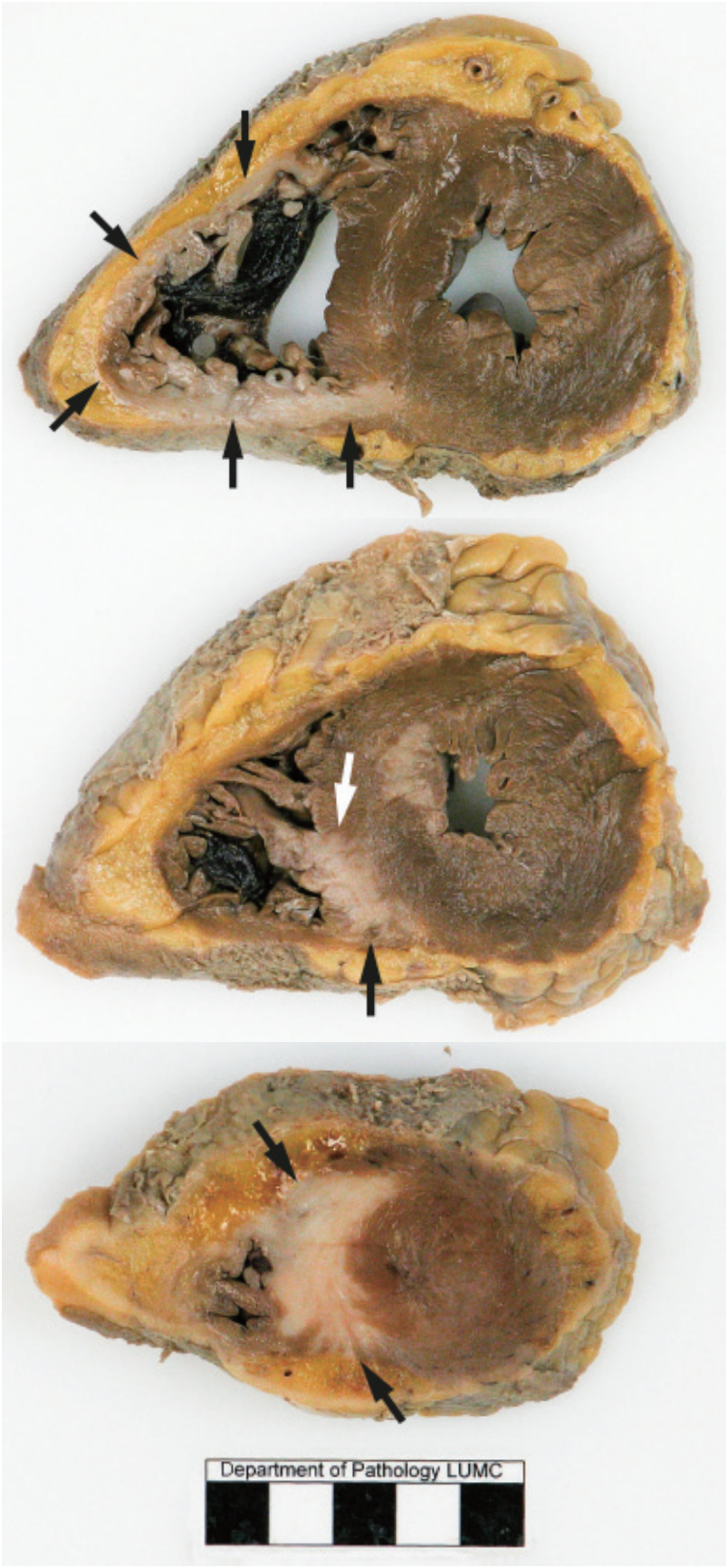

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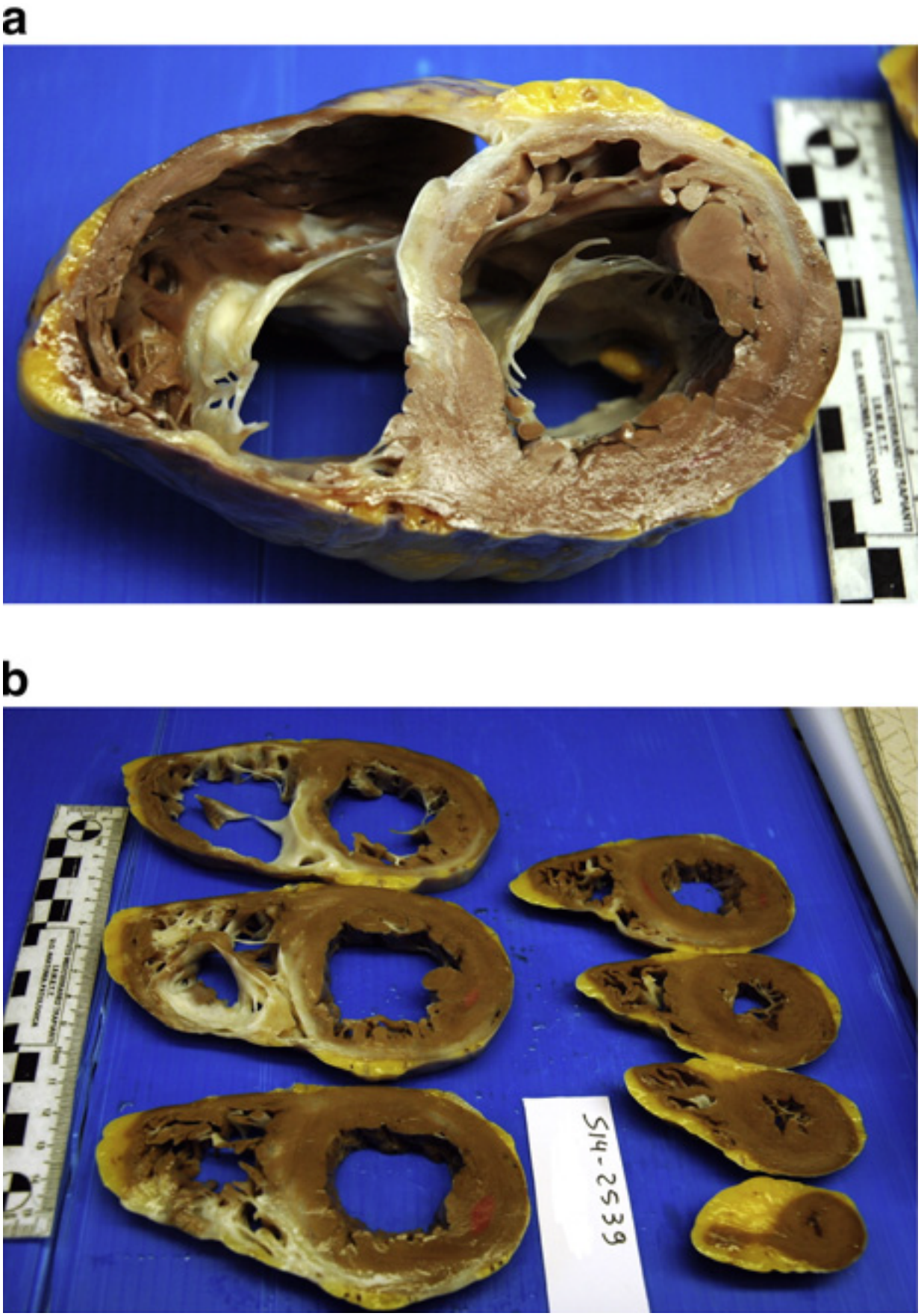

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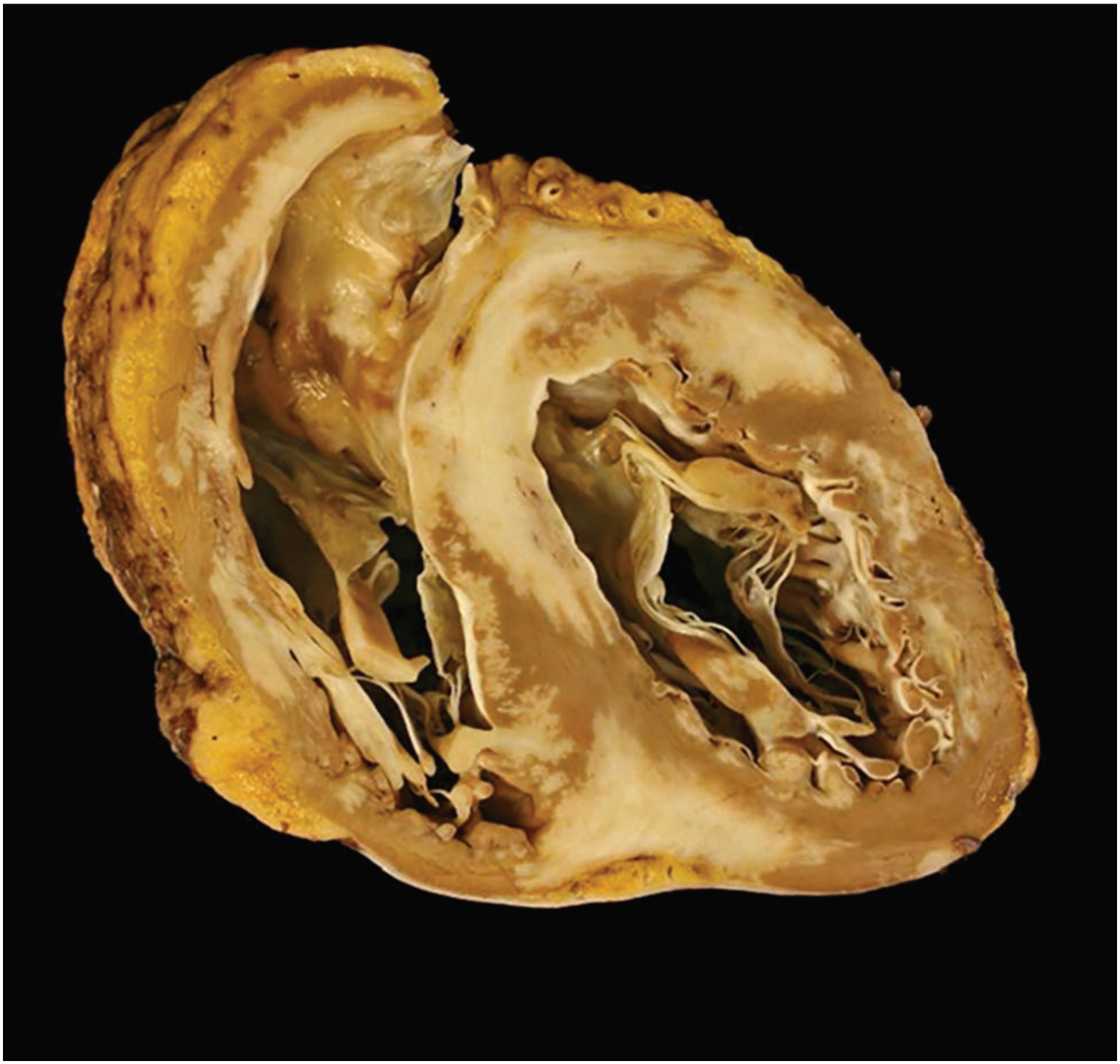

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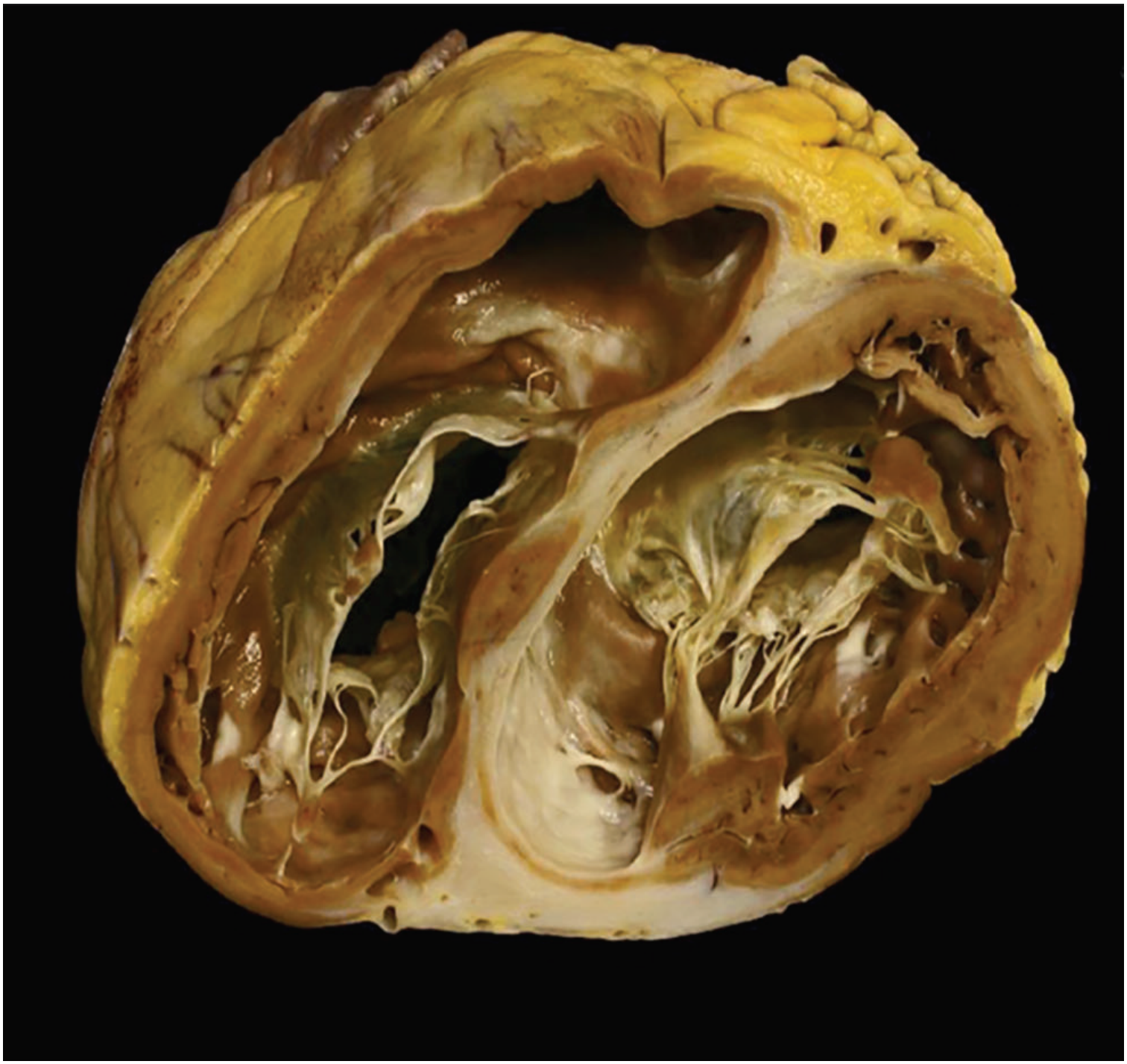

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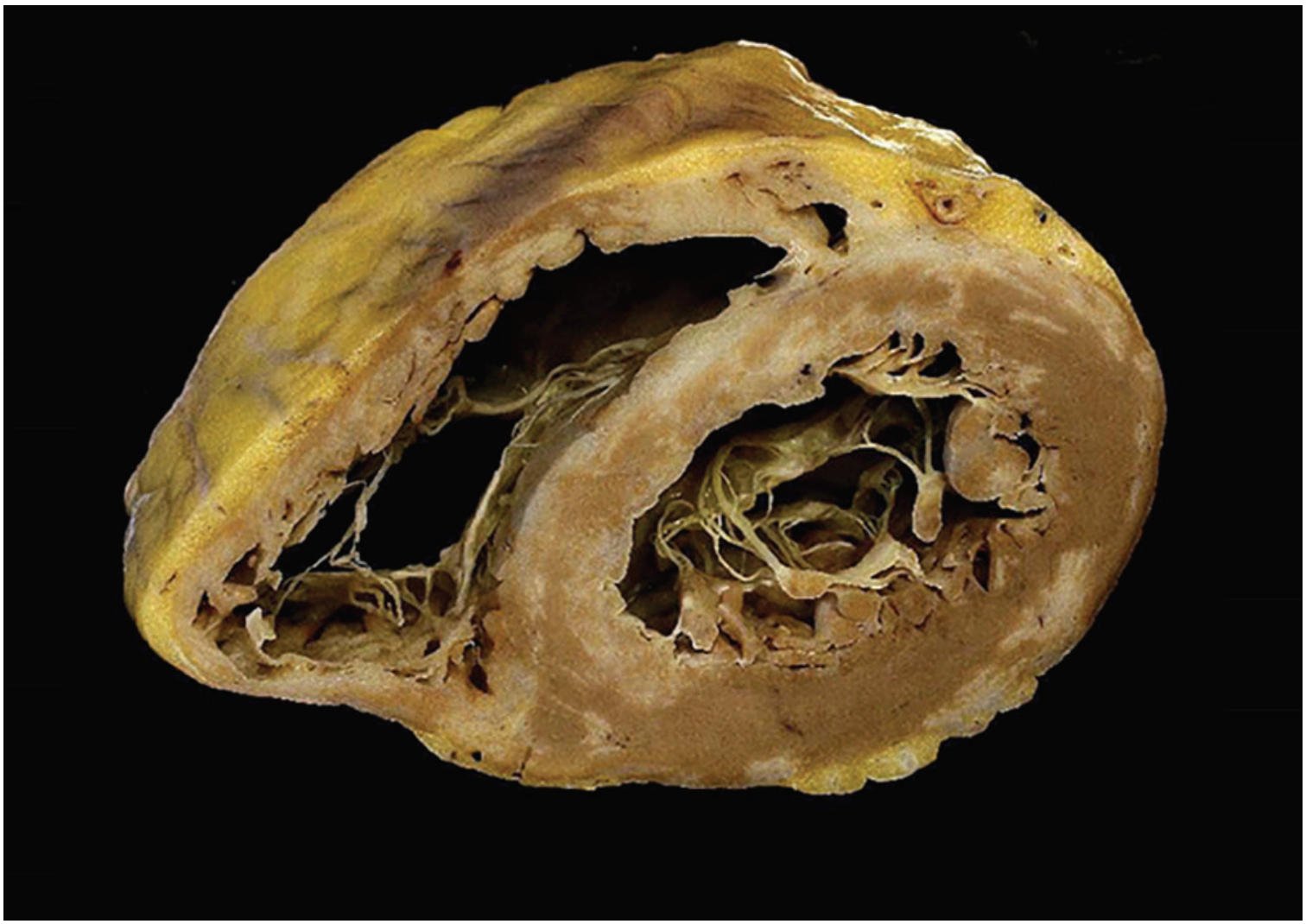

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