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Lymphocytic myocarditis: A histopathologic definition and classification from the society for cardiovascular pathology and association for European cardiovascular pathology. II: Surgical and autopsy specimens

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ABSTRACT

Background and aim: Lymphocytic myocarditis, characterized by lymphocyte-predominant myocardial inflammation with associated myocyte injury, is a term that has decades-old histopathologic criteria when encountered on endomyocardial biopsy. However, the interpretation of non-biopsy specimens such as surgical resections and autopsy samples has lacked standardized histopathologic criteria, despite their growing clinical and forensic relevance. The aim was to develop and establish criteria for the diagnosis and classification of lymphocytic myocarditis in non-biopsy ventricular myocardial specimens.

Methods and results: An international panel of cardiovascular pathologists representing the Society for Cardiovascular Pathology (SCVP) and the Association for European Cardiovascular Pathology (AECVP) developed a new classification system, which was completed at a final meeting in the Seaport area of Boston. These "Seaport" criteria for non-biopsy specimens formally define lymphocytic myocarditis as myocardial inflammation predominantly composed of lymphocytes, accompanied by myocyte injury not attributable to other causes. Recommendations address specimen type, technical handling, diagnostic thresholds, and qualifiers of chronicity. Diagnostic categories include active myocarditis and lymphocytic infiltrate of uncertain significance (LIUS). The document also outlines the interpretive challenges in attributing causality in autopsy settings, provides guidance on the use of ancillary techniques, and highlights the limitations of current histopathologic approaches.

Conclusion: These consensus-based criteria offer a standardized framework for diagnosing lymphocytic myocarditis in non-biopsy specimens. Adoption of these guidelines is expected to improve diagnostic consistency, enhance research comparability, and inform clinical and forensic evaluations. Future efforts should aim to refine definitions of myocyte injury, validate ancillary techniques, and elucidate the clinical significance of inflammation in the absence of injury.

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1. Introduction

Myocarditis broadly refers to non-ischemic myocardial inflammation and can be categorized by two related parameters – etiology and histologic pattern. Lymphocytic myocarditis, one of the most frequently encountered patterns, is most usually attributed to unproven viral infections although other infectious and non-infectious underpinnings have been described. The clinical presentation of myocarditis may range from absence of symptoms to sudden death. Histological tissue diagnosis of myocarditis has been considered the gold standard.

In 1987, the Dallas Criteria established the histopathologic findings defining a diagnosis of lymphocytic myocarditis on endomyocardial biopsy specimens, but did not address whether or how these criteria should be used on larger (non-biopsy) samples [1]. While the specificity of biopsy specimen for myocarditis is incredibly high, biopsies are limited in several important ways. These include sensitivity (sampling) as well as circumstances (not all sampling of the heart is by way of biopsy).

Endomyocardial biopsy specimens are generally small and regionally limited, usually to the right-sided ventricular septum. Thus, a negative endomyocardial biopsy specimens cannot definitively exclude the possibility of myocarditis. Pathologists frequently are asked to look at myocardium derived from a variety of non-biopsy procedures, such as explant, myectomy specimens, or apical core resections. Inflammation can be encountered in these specimens and may explain underlying cardiac dysfunction. Finally, in the post-mortem setting, hearts evaluated at autopsy may contain inflammation that should be characterized in a systematic way to allow for proper contextualization [2]. The recent COVID-19 pandemic underscored this latter need as public health decisions were being made based on data that lacked consistent definition and diagnostic thresholds [3].

In 2022, the Society for Cardiovascular Pathology (SCVP) and the Association for European Cardiovascular Pathology (AECVP) came together and agreed that there was a need to codify the diagnosis of lymphocytic myocarditis in non-biopsy samples. A series of meetings over the next two years culminated in a joint consensus meeting of the two societies in March 2024 in Baltimore, MD and completed at a final meeting in the Seaport area of Boston in March 2025. Herein is presented the proceeding and general consensus reached at this meeting regarding the diagnosis of lymphocytic myocarditis in non-biopsy samples, including those derived at surgery or autopsy.

2. Methods

An international team of cardiovascular pathologists came together to thoroughly review the existing literature and generate an improved approach to diagnosing lymphocytic myocarditis. This team was divided into two subgroups, one charged with establishing criteria for diagnosis of lymphocytic myocarditis on endomyocardial biopsies and the other subgroup was to establish criteria for the diagnosis of lymphocytic myocarditis on surgical and autopsy specimens. The results of the former subgroup are published separately in this journal [4]. The latter subgroup consisted of 11 pathologists representing ten institutions across seven countries and are members of either the Association for European Cardiovascular Pathology (AECVP) or the Society for Cardiovascular Pathology (SCVP).

The panel of experts conducted a comprehensive literature review on myocarditis in non-biopsy specimens to analyze current practices and foster debate on updated recommendations. The databases used included PubMed, Web of Science, The Cochrane Library, and Google Scholar. Subgroups of experts focused on specific topics such as autopsy, biomarkers, case reports, consensus documents, COVID-19, drugs, cardiac explant pathology, immunohistochemistry, and related review articles. Virtual meetings were organized to summarize the collected papers, and a list of questions to be evaluated was developed following preliminary meetings (available in the Supplemental material).

A modified Delphi method was used to administer the questionnaire [5]. Three rounds of the Delphi exercise were conducted. During the first round, the eleven pathologists were administered the same survey with anonymized data collection, and responses were provided in an open-answer format. Virtual meetings with on-camera discussions of the results were organized between the first and second rounds. Before the second round, the question list was revised to obtain yes or no answers from the pathologists. During the second round, participants ranked the revised questions, with optional commentary particularly for statements without agreement during the previous round. Replies were again anonymously collected. After the second round, discrepancies were discussed during a virtual meeting. A final virtual meeting was then organized, in which agreement was eventually reached among all the experts on every statement. The questions from the Delphi questionnaires are available in the supplemental file.The statements from the Delphi rounds were then compiled as a list of recommendations. A hybrid (in-person and virtual) meeting was jointly organized with the support of the two international Societies (AECVP and SCVP) on March 23, 2024, in Baltimore (MD, USA), to present and broadly discuss preliminary recommendations. Feedback was gathered from the audience, which included multidisciplinary professionals such as basic scientists, cardiologists, radiologists, and pathologists not dedicated to cardiovascular specimens.

3. Criteria

3.1. Specimen types

The criteria are meant to encompass two broad categories of specimens that include ventricular myocardium, those derived from surgical (non-biopsy) resection and those procured at autopsy (Table 1). These include four basic specimen types: autopsy hearts, surgically explanted hearts, septal myectomy, and apical core resections (Fig. 1). Atrial specimens (e.g., atrial appendages, reduction atrioplasties, atrial septectomies, etc.) are specifically excluded, because of the uncertain clinical significance of inflammation within atrial myocardium. Significant variability exists across these specimen types in terms of both the amount of tissue available for evaluation as well as the location within the heart from which it is taken. Autopsy, for example, typically affords for maximal evaluation of myocardium, limited only by practical constraints of how much myocardium is evaluated by the pathologist. At the other end of the spectrum, sub-total myocardial resections such as those taken out in installation of a ventricular assist device (apical core resection) or to relieve outflow tract obstruction (septal myectomy) are more limited and variable in both myocardium amount and location.

3.2. Technical requirements

Processing and handling ventricular myocardial specimens is generally in accord with previously established recommendations [6,7]. This section will focus on the minimum amount of ventricular myocardium that is recommended to be evaluated in each of the various specimen types to reasonably exclude the possibility of lymphocytic myocarditis (summarized in Table 1). Importantly, the recommendations below are *minimums* and additional samples should be considered in clinically compelling cases where myocarditis is a high probability. A tiered approach can also be employed, wherein these minimums are initially processed, and additional sections are evaluated if the first round is not conclusive diagnostically.

For autopsy and explant specimens, a minimum of six full-thickness (endocardium to epicardium) sections of ventricular myocardium should be evaluated histologically (Fig. 2). If gross abnormalities are observed, the sampling should include such regions. Multiple right ventricular sections may be combined into a single block. Sampling of the atrioventricular conduction system may be included but is not mandatory. In accord with the tiered sampling approach described

Table 1
Expert consensus criteria for diagnosis of lymphocytic myocarditis in non-biopsy ventricular samples.

Tissue source	Technical requirements	Definition of lymphocytic myocarditis	Extent
Autopsy Explant Apical Core Septal Myectomy	6 full-thickness sections in 5 or 6 blocks* Entirely submitted (to visualize epicardium to endocardium) 2 blocks of myocardium	Myocardial lymphocytic inflammation with myocyte injury** that is not explained by another cause (ischemia, trauma, foreign body, amyloid, etc.). Myocyte injury must be distinct from changes seen in non-inflamed areas and may consist of: • myocytolysis • single-cell hypereosinophilia • nuclear karryorrhexis/karyolysis • sarcolemmal scalloping • myocyte dropout • vacuolar degeneration	Focal: single focus Diffuse: ≥50 % area of a single block involved by confluent myocarditis Multifocal: more than a single focus but <50 % area of a single block involved by confluent myocarditis

* Minimum of 1 short-axis slice (taken at mid-ventricular level) should be saved for additional processing.
** In the absence of myocyte injury, the term "lymphocytic infiltrate of undetermined significance" (LIUS) should be used.

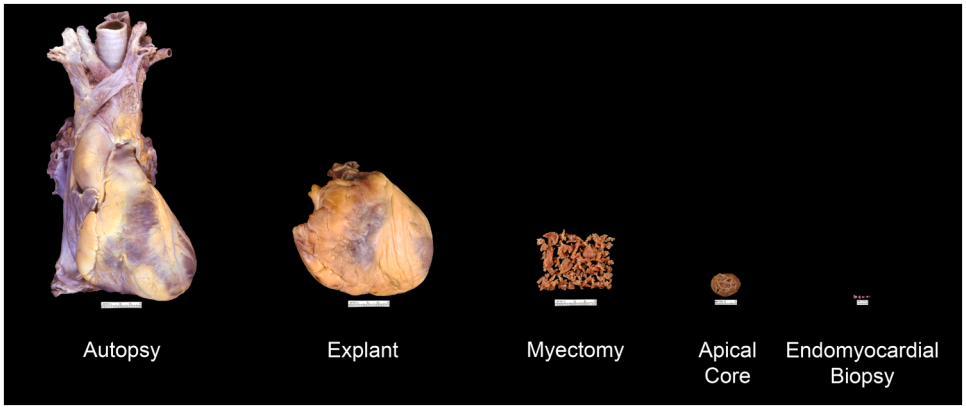

Fig. 1. Ventricular myocardial specimen size comparison. The tissue available for review varies greatly from the entire ventricular mass, available in autopsy and explant specimens and smaller amounts available as a result of myectomy or apical core resections. Significantly more myocardium is available for review than with endomyocardial biopsy.

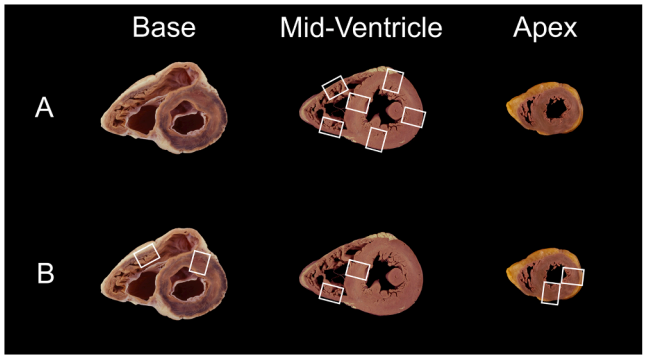

Fig. 2. Sampling of autopsy or explant specimens. A minimum of six full-thickness (epicardium to endocardium) sections of ventricular myocardium should be sampled for histologic examination to adequately exclude a diagnosis of lymphocytic myocarditis. These sections may be taken from a (A) single ventricular level or (B) scattered across multiple ventricular levels.

above, a minimum of a single mid-ventricular short-axis section should be retained for additional sampling, as indicated.

Evaluation of septal myectomy specimens should generally include a minimum of two cassettes of myocardium, depending on the size of the sample. Apical core resections should be entirely submitted as cross-sections to visualize epicardium, myocardium and endocardium.

3.3. Criteria

Lymphocytic myocarditis is defined as myocardial lymphocyte-predominate inflammation with myocyte injury that is not explained by another cause (e.g., ischemia, trauma, foreign body, amyloid, etc.) (Fig. 3). When identified, the term *active lymphocytic myocarditis* should be invoked.

In addition to the diagnosis, extent should also be described as focal, multifocal or diffuse. *Focal* is to be used when a single focus of lymphocytic myocarditis is identified that does not involve ≥50 % of the area of myocardium on the examined tissue section. *Multifocal* is to be used when two or more non-contiguous foci are identified (on a single tissue section or across multiple tissue sections), but the areas

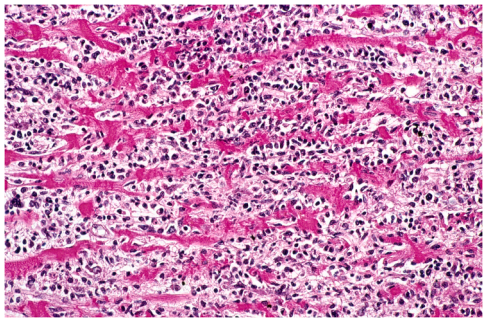

Fig. 3. Active lymphocytic myocarditis. There is diffuse lymphocytic infiltrate with extensive myocyte injury.

collectively involve <50 % area of the examined tissue section. *Diffuse* is to be used when ≥50 % of the area of a single tissue section is involved by active lymphocytic myocarditis.

3.4. Myocyte injury

A spectrum of myocytologic changes are indicative of injury. Findings such as sarcolemmal scalloping, myocyte hypereosinophilia, nuclear pyknosis (shrinkage, with chromatin condensation) karryorrhexis/karyolysis (nuclear fragmentation/dissolution), vacuolar degeneration and myocytolysis (disruption of the sarcolemma) are all considered sufficient to establish injury. An atlas of changes that were agreed to be in keeping with myocyte injury is included in Fig. 4.

3.5. Inflammation without myocyte injury

Identification of lymphocytic infiltrate within the myocardium in the absence of myocyte injury (Fig. 5) should prompt careful review for myocarditis elsewhere in the heart. This may include increasing the number of examined tissue sections. If myocyte injury cannot be confidently identified, the term *lymphocytic infiltrate of uncertain significance (LIUS)* is recommended. Generally speaking, lymphocytes in areas of fibrosis, fat, or in blood vessels/lymphatics (Fig. 6) should not be regarded as any type of myocarditis.

3.6. Other cell types

The natural history of lymphocytic myocarditis is generally thought to begin with a robust lymphocytic infiltrate that will resolve over variable periods of time. During this resolution, the nature of the infiltrate changes as we see other leukocytes (e.g., histiocytes) and granulation tissue move into the injured areas of myocardium. Additionally, medical therapies may change the cellular constituency of the process, possibly increasing eosinophils (in the case of vasopressors or diuretics) or other cell types. The precise number of other inflammatory cells that should trigger consideration of other entities, such as eosinophilic myocarditis, has not been definitively established. Nevertheless, the major cell type should tend to define the infiltrate and other cell types can be mentioned in a comment.

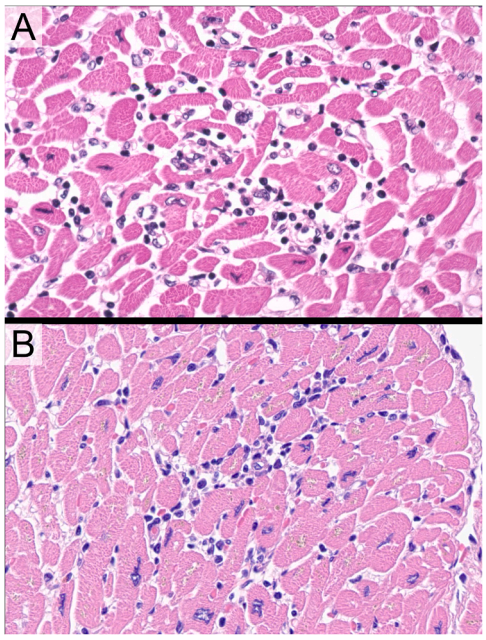

Fig. 5. Lymphocytic infiltrate of uncertain significance (LIUS). **(A** and **B)** Interstitial lymphocytes are present but not associated with myocyte injury in two different cases.

3.7. Ancillary techniques

Immunohistochemistry (IHC) was extensively discussed and debated within the expert group, as well as at the larger consensus meeting. Immunohistochemistry is likely to increase the diagnostic yield of lymphcytic type of myocarditis, but the cost and access limitations, particularly in the forensic setting, have made it difficult to mandate

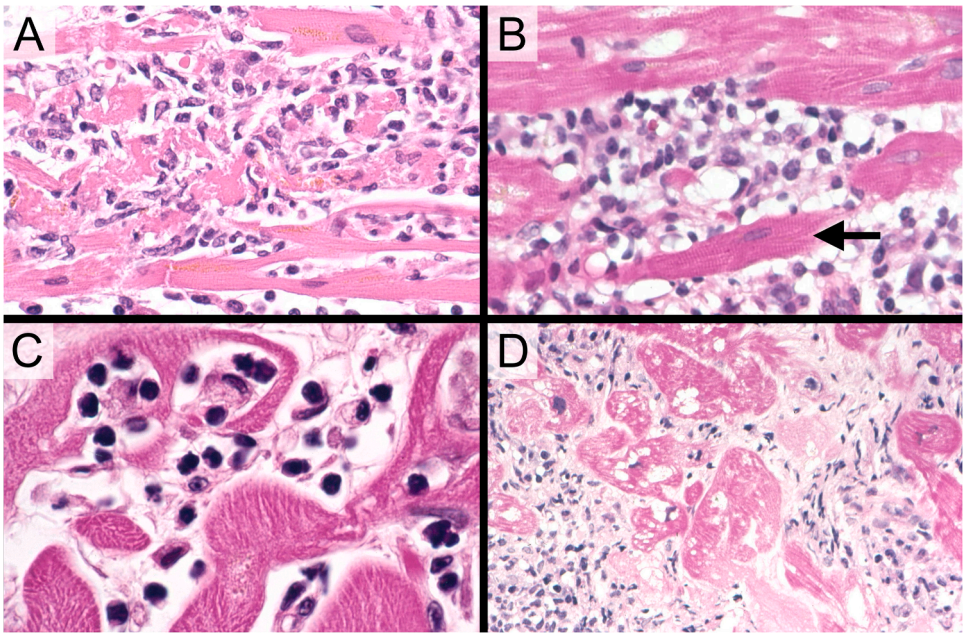

Fig. 4. Myocyte injury. Examples of myocyte injury include: **A)** myocytolysis, where the infiltrate is associate with overt breakdown of myocyte structure; **B)** scalloping of the sarcolemma with sharp and irregular borders (arrow) imparted by the lymphocytic infiltrate (the myocyte also exhibits hypereosinophilia when compared with myocytes at the top of the photomicrograph; **C)** lymphocyte internalization, characterized by lymphocytes present within the sarcoplasm of the myocytes; and **D)** vacuolar degeneration with prominent vacuoles contained within the cytoplasm of the myocytes.

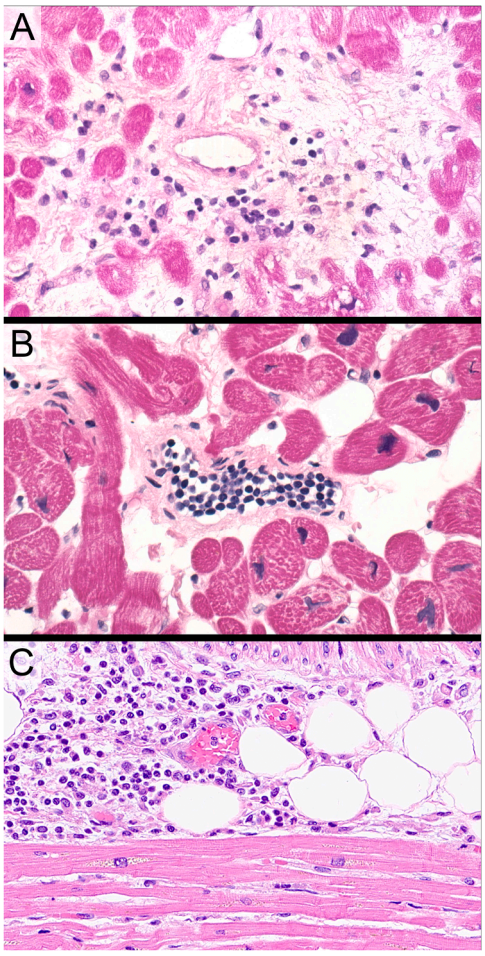

Fig. 6. Non-myocarditis mimics. Lymphocytes may be seen in **A)** areas of fibrosis **B)** within blood vessels or lymphatics and/or **C)** fat. None of these should be regarded as myocarditis.

such techniques in the diagnosis of myocarditis for autopsy and surgical samples. Additionally, the data precise lymphocyte counts in this setting is very much lacking. Further still, there was a general belief that the larger sampling size of surgical and autopsy specimens allowed for more thorough evaluation of a specific patient, perhaps rendering IHC less necessary at this time. Other technologies, such as troponins, imaging, and molecular genetics (specifically for viral nucleic acid detection) were also discussed, but believed to nacent to recommend incorporation into the criteria at this time [8].

4. Temporal qualifiers for myocarditis

The term *chronic* myocarditis has been variably used by pathologists to describe myocarditis that has histopathologic features of chronicity, typically appropriately distributed replacement-type fibrosis. The presence of granulation tissue also implies some chronicity which some have termed *subacute* myocarditis. Because granulation tissue and fibrosis are not specific to myocarditis, the pattern and distribution of injury as well the clinical circumstances are often used as adjunct parameters when postulating the etiology.

The distinction between acute, subacute, and chronic myocarditis is not always clear-cut. Nevertheless, these temporal qualifiers can have clinical relevance and may guide interpretation. We recommend the following framework when lymphocytic myocarditis is identified:

- **Acute lymphocytic myocarditis**: No granulation tissue is present.
- **Subacute lymphocytic myocarditis**: Granulation tissue is present.
- **Chronic lymphocytic myocarditis**: Mature, replacement-type interstitial fibrosis is observed.

Over time, lymphocytic myocarditis may "burn out," leaving behind only residual scarring. In such cases, it can be difficult to confidently attribute the scarring to a prior inflammatory process no longer present. Nonetheless, the *distribution* of scarring can offer diagnostic clues. For example, myocarditis-related fibrosis often favors subepicardial regions, whereas ischemic injury typically originates in the subendocardium and follows the vascular territories of the epicardial coronary arteries. Additionally, ischemic fibrosis may spare the immediate subendocardial myocytes due to their proximity to oxygen-rich blood in the cardiac chambers—this is not a feature of myocarditis.

Chronic myocarditis is typically associated with persistent myocardial inflammation involving lymphocytes, macrophages, and occasionally eosinophils. This sustained inflammatory response leads to ongoing myocyte injury, necrosis, and fibrotic remodeling. As myocytes are progressively lost, the myocardium may undergo structural changes including biventricular dilation, hypertrophy, and interstitial fibrosis. These alterations can impair cardiac function and potentially lead to heart failure. In such cases, descriptive diagnostic terms such as **"findings suggestive of prior myocarditis-related injury"** or **"chronic myocarditis-related heart disease"** may be appropriate, depending on the degree of diagnostic certainty.

5. Relationship to cause and manner of death

When a diagnosis of myocarditis is established at autopsy, the pathologist must determine whether the demonstrated myocarditis is causal, contributory, or of no significance at all for the cause of death. The relation between histopathological findings and clinical symptoms is however not straightforward.

Intuitively, more extensive disease correlates with more profound clinical symptoms such as congestive cardiac failure and a higher risk of (potentially fatal) cardiac arrhythmias. This is endorsed by the AECVP Guidelines for autopsy investigation of sudden cardiac death, which states that "fulminant' or "multifocal" myocarditis can be generally accepted as a reliable cause of death, especially in absence of other relevant findings [9]. Various papers that correlated extent of inflammation with reported cause of death support this recommendation [2,10,11]. However, less extensive (focal) myocarditis is not necessarily unrelated to the cause of death, since foci of myocarditis are assumed to have arrhythmogenic potential, especially when involving parts of the conduction system.

At the same time, focal and multifocal myocarditis are relatively frequent findings at autopsy, due to the larger amount of tissue available for examination [2]. Such a focal or multifocal myocarditis can be entirely incidental, as shown in papers that studied myocardial inflammation in individuals with a clear alternative cause of death [10]. Focal and multifocal myocarditis should therefore not be overinterpreted as necessarily causing or contributing to death [2]. There are currently no other histological features that help to differentiate between an incidental and significant (multi)focal myocarditis.

Various factors can further confound the interpretation of myocarditis. For instance, cardiopulmonary resuscitation, cardiac arrhythmias and catecholamine surge can all induce myocyte injury, which can attract inflammatory cells if there is sufficient interval survival. Furthermore, drugs such as cocaine and anti-psychotics can cause inflammation in the heart with similarly ambiguous significance [12,13]. A number of genetic heart muscle diseases (cardiomyopathies) may also present in the early phases as focal or recurrent myocarditis [14].

Determining the cause of death in a case with histopathological myocarditis generally requires a comprehensive consideration of all available evidence. This will often include a complete autopsy with histology of all major organs and appropriate ancillary studies (including toxicology).

Ante mortem data should at least include the circumstances surrounding death and the medical history of the deceased. A history of a recent viral illness, or symptoms such as chest pain, fatigue, shortness of breath, palpitations, syncope, and fever make a diagnosis of fatal myocarditis more likely. A sudden unexpected death in an apparently healthy individuals is more in keeping with a cardiac arrhythmia. If applicable, clinical data such as ECGs, cardiac MRI, echocardiograms and/or troponin levels must be made available.

6. Other considerations

One major limitation of the approach in this document is the consideration of lymphocytic myocarditis as a defined disease process distinct from myocarditis with significant amounts of other cell types such as eosinophils and giant cells. When inflammatory heart conditions are studied by etiologic group rather than inflammatory pattern, for each etiology there is often a spectrum of patterns of inflammatory infiltration. For example, immune checkpoint inhibitor associated myocarditis, SARS-CoV-2 myocarditis, and acute cellular allograft rejection may all be lymphocytic or contain significant numbers of eosinophils [15–17]. In some instances, differences in inflammatory pattern are likely more a reflection of pathologic grade or severity than of etiology. Most studies on idiopathic (presumed viral) lymphocytic myocarditis are likely encompassing myocarditis of many different etiologies making cross-study comparisons difficult. More studies with a focus on defined etiologic types of myocarditis are clearly needed.

The current approach in this document relies solely on evaluation of hematoxylin and eosin (H&E) stained slides. This approach can be highly subjective with many practicing pathologists lacking formal training to evaluate for myocarditis [18]. Formal training in cardiovascular pathology needs to be expanded. Also, less subjective, more affordable, and universally available methods to evaluate for myocardial inflammation and myocyte injury are needed, and pathology departments and forensic offices need to be adequately funded to be able to utilize these techniques.

While this study attempts to provide a unified approach to all non-biopsy specimens from apical cores to autopsies, it must be remembered that the context of the pathologic changes may be very important when considering their significance. For example, a single focus of myocarditis in an autopsy case with 20 blocks of heart tissue will likely not have the same significance as a single focus of myocarditis in an apical core specimen with 1 block of heart tissue in a patient undergoing urgent ventricular assist device placement for acute idiopathic systolic heart failure. Likewise, atrial myocardial resections were entirely excluded from consideration for this manuscript. Further detailed studies characterizing myocarditis in each type of myocardial resection are needed.

7. Future directions

There have been several projects, including this one, aimed at evaluating the histologic findings of myocardial inflammation and injury in myocarditis and relating these findings to clinical significance [19]. However, there are general limitations to current histologic methods of study:

1. **Sampling Error**: Myocarditis is usually patchy, and its distribution varies greatly. Even with numerous large histologic sections, regions of inflammation and injury may be missed.
2. **Non-Specific Findings**: It is established that character and pattern of inflammation correlate with certain etiological groups (e.g., infectious, auto-immune, hypersensitivity, etc.) but the findings of inflammation and injury are ultimately non-specific. Other ancillary diagnostic techniques will need to be developed or refined to better understand the pathogenesis of myocarditis.
3. **Microscopic Evaluation Limitations**: Purely microscopic evaluation does not provide insight into possible environmental, genetic, or molecular factors that might be modulating the inflammatory process.
4. **Correlation with Clinical Findings**: There is not a consistent correlation between microscopic findings and clinical findings and, microscopic findings are therefore of limited prognostic value. The inflammatory cells present may be proinflammatory or directed towards healing with fibrosis.

The above general limitations are inherent to histologic study. There are also limitations to the specific criteria outlined in this document that should set the stage for study in the near-term. These include a better understanding of the phenomenon of LIUS, the role of other cell types (specifically histiocytes) in lymphocytic myocarditis and whether immunohistochemistry can improve the diagnosis of lymphocytic myocarditis in non-biopsy samples. The routine use of immunohistochemistry in biopsy samples, as being recommended in the contemporaneously published article on biopsy criteria for lymphocytic myocarditis, will likely provide valuable insights. These combined histologic limitations direct attention towards other diagnostic modalities to better understand myocarditis.

Significant progress has been made in detecting virus in the heart [20,21]. However, it has been recognized that the presence of a virus does not necessarily mean it is causing the inflammation and tissue injury. Moreover, it is assumed that at least a subset of clinically relevant myocarditis is mediated by immunological cross-reactivity instead of direct infection [14]. Methods to better understand the inflammatory process are needed. Some molecular/genetic methods have been applied to study non-infectious causes of myocarditis at the molecular level rather than simply the histologic level [22].

Novel methods applying systems biology and artificial intelligence will likely further contribute to our understanding of what is happening in the myocardium and in individuals afflicted with myocarditis. Animal models that more closely reflect the human disease need to be developed for investigational studies. Additionally, the emerging area of spatial transcriptomics may provide critical insights on the relationship between inflammation and myocyte injury – particularly injury for which there is not a clear morphologic counterpart.

New and better ways to understand, diagnose, and treat myocarditis are needed and it will likely require a multidisciplinary approach. In many respects, this is already occurring through the shift away from biopsy towards imaging to diagnose myocarditis [23,24]. It is possible that development of novel radiologic tracers could one day set the stage for not only identifying inflammation but also characterizing it by cell type [25]. This approach could lead to earlier and more specific diagnoses, as well as more targeted therapy.

8. Conclusions

The above-presented criteria represent a common framework on which to evaluate non-biopsy ventricular samples for lymphocytic myocarditis and formulate diagnostic reports. We acknowledge that that there is a paucity of data that informs these practices, but it is our sincere hope that these criteria will allow for a common language facilitating study that will allow for refinement. Certainly, a better understanding of the significance of inflammation without overt myocyte injury is essential. For that matter, it is also crucial to refine the definition of myocyte injury and create more robust and reproducible criteria.

These criteria are notably different than those described in the companion paper published in this edition of *Cardiovascular Pathology* [4]. While immunohistochemical detection of T-lymphocytes is integral to the biopsy formulation, it is meant to overcome the sampling limitations inherent to the biopsy procedure. Further, the lack of widespread availability of immunohistochemistry (particularly in the forensic setting) informed our approach in this regard.

The significance of these findings must also be a subject of future study. For instance, how much lymphocytic myocarditis must be present to attribute to death or symptoms is not clear. Similarly, the significance of LIUS (as the name implies) is also unknown. Resources directed at these areas, as well as additional formal training in cardiovascular pathology is strongly recommended.

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CRediT authorship contribution statement

Joseph J. Maleszewski: Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Jytte Banner:** Writing – review & editing. **Hans de Boer:** Writing – review & editing. **Monica De Gaspari:** Writing – review & editing. **Michael C. Fishbein:** Writing – review & editing. **Sarah Parsons:** Writing – review & editing, Conceptualization. **Barbara Sampson:** Writing – review & editing. **Mary N. Sheppard:** Writing – review & editing. **Allard C. Van der Wal:** Writing – review & editing. **James R. Stone:** Writing – review & editing. **Katarzyna Michaud:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

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References

[1] Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio Jr JJ, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol 1987;1(1):3–14.
[2] Oyarzun A, Parsons S, Bassed R. Myocarditis in the forensic setting – a review of the literature. Cardiovasc Pathol 2023;62:107475.
[3] Maleszewski JJ, Young PM, Ackerman MJ, Halushka MK. Urgent need for studies of the late effects of SARS-CoV-2 on the cardiovascular system. Circulation 2021;143(13):1271–3.
[4] Halushka MK, d'Amati G, Bois MC, Fallon JT, Giordano C, Klingel K, et al. Lymphocytic myocarditis: a histopathologic definition and classification from the Society for Cardiovascular Pathology and Association for European Cardiovascular Pathology. I: endomyocardial biopsy. Cardiovasc Pathol 2025.
[5] Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lázaro P, et al. The RAND/UCLA appropriateness method user's manual. Santa Monica, CA: RAND Corporation; 2001.
[6] Kelly KL, Lin PT, Basso C, Bois M, Buja LM, Cohle SD, et al. Sudden cardiac death in the young: a consensus statement on recommended practices for cardiac examination by pathologists from the Society for Cardiovascular Pathology. Cardiovasc Pathol 2023;63:107497.
[7] Stone JR, Basso C, Baandrup UT, Bruneval P, Butany J, Gallagher PJ, et al. Recommendations for processing cardiovascular surgical pathology specimens: a consensus statement from the Standards and Definitions Committee of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology. Cardiovasc Pathol: Off J Soc Cardiovasc Pathol 2012;21(1):2–16.
[8] Michaud K, Jacobsen C, Basso C, Banner J, Blokker BM, de Boer HH, et al. Application of postmortem imaging modalities in cases of sudden death due to cardiovascular diseases-current achievements and limitations from a pathology perspective: endorsed by the Association for European Cardiovascular Pathology and by the International Society of Forensic Radiology and Imaging. Virchows Arch 2023;482(2):385–406.
[9] Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch 2017;471(6):691–705.
[10] Du Long R, Fronczek J, Niessen HWM, Van Der Wal AC, De Boer HH. The histopathological spectrum of myocardial inflammation in relation to circumstance of death: a retrospective cohort study in clinical and forensic autopsies. Forensic Sci Res 2022;7(2):238–46.
[11] Kitulwatte ID, Kim PJH, Pollanen MS. Sudden death related myocarditis: a study of 56 cases. Forensic Science. Med Pathol 2010;6(1):13–9.
[12] Fineschi V, Wetli CV, Paolo MD, Baroldi G. Myocardial necrosis and cocaine. Int J Leg Med 1997;110(4):193–8.
[13] Kilian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999;354(9193):1841–5.
[14] Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol 2021;18(3):169–93.
[15] Champion SN, Stone JR. Immune checkpoint inhibitor associated myocarditis occurs in both high-grade and low-grade forms. Mod Pathol 2020;33(1):99–108.
[16] Bearse M, Hung YP, Krauson AJ, Bonanno L, Boyraz B, Harris CK, et al. Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. Mod Pathol 2021;34(7):1345–57.
[17] Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005;24(11):1710–20.
[18] Thiene G, Veinot JP, Angelini A, Baandrup UT, Basso C, Bruneval P, et al. AECVP and SCVP 2009 recommendations for training in Cardiovascular pathology. Cardiovasc Pathol 2010;19(3):129–35.
[19] Ammirati E, Veronese G, Bottiroli M, Wang DW, Cipriani M, Garascia A, et al. Update on acute myocarditis. Trends Cardiovasc Med 2021;31(6):370–9.
[20] Nguyen Y, Renois F, Leveque N, Giusti D, Picard-Maureau M, Bruneval P, et al. Virus detection and semiquantitation in explanted heart tissues of idiopathic dilated cardiomyopathy adult patients by use of PCR coupled with mass spectrometry analysis. J Clin Microbiol 2013;51(7):2288–94.
[21] Majumdar R, Vrana JA, Koepplin JW, Milosevic D, Roden AC, Garcia JJ, et al. SARS-CoV-2 RNA detection in Formalin-fixed paraffin-embedded (FFPE) tissue by droplet digital PCR (ddPCR). Clin Chim Acta Int J Clin Chem 2022;532:181–7.
[22] Bruestle K, Hackner K, Kreye G, Heidecker B. Autoimmunity in acute myocarditis: how immunopathogenesis steers new directions for diagnosis and treatment. Curr Cardiol Rep 2020;22(5):28.
[23] Urzua Fresno C, Sanchez Tijmes F, Shaw KE, Huang F, Thavendiranathan P, Khullar S, et al. Cardiac imaging in myocarditis: current evidence and future directions. Can Assoc Radiol J 2023;74(1):147–59.
[24] Cihakova D, Shi Y, Adhikari B, Bandettini WP, Cunningham MW, Danthi N, et al. Meeting the challenges of myocarditis: new opportunities for prevention, detection, and intervention-A report from the 2021 National Heart, Lung, and Blood Institute Workshop. J Clin Med 2022;11(19):5721.
[25] Lucinian YA, Martineau P, Abikhzer G, Harel F, Pelletier-Galarneau M. Novel tracers to assess myocardial inflammation with radionuclide imaging. J Nucl Cardiol 2024;42:102012.