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PERSPECTIVE

Discordance Between Morphology and Molecular Findings in Dermatopathology: A Perspective on Diagnostic Integration

Cornelia Sigrid Lissi Müller[1,2]

[1]MVZ for Histology, Cytology and Molecular Diagnostics Trier, Trier, Germany | [2]Faculty of Medicine, Saarland University, Homburg, Germany

Correspondence: Cornelia Sigrid Lissi Müller (cornelia.mueller@patho-trier.de)

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Molecular pathology has become an increasingly important component of dermatopathologic diagnostics, with assays widely used to support, refine, or exclude diagnostic considerations derived from clinical and histopathological assessment. While their expanding availability and technical sophistication have improved diagnostic precision in selected contexts, they have also introduced interpretative challenges, particularly when molecular findings are discordant with morphological features and clinical presentation [1, 2]. Dermatopathology has traditionally been an integrative discipline, combining clinical information, histopathological evaluation, and ancillary techniques. Molecular pathology was introduced as an additional diagnostic tool, intended to complement morphology rather than replace it [3]. In routine practice, however, molecular results are often perceived as highly objective and reproducible, which may lead to an unintended expectation of diagnostic finality [4]. This perception can become problematic when molecular findings do not align with established morphological patterns or with the clinical scenario. Diagnostic discordance between morphology and molecular pathology is a frequent experience in daily dermatopathologic practice [5, 6]. Representative examples from routine diagnostics are summarized in Table 1. Negative or inconclusive molecular results are encountered across a broad spectrum of conditions, including inflammatory dermatoses, lymphoproliferative disorders, viral-associated epithelial lesions and mesenchymal or melanocytic neoplasms. In many of these cases, histopathology demonstrates characteristic and reproducible features, while molecular testing fails to detect a corresponding alteration. Such discrepancies do not necessarily indicate diagnostic error. Rather, they reflect intrinsic biological and methodological limitations. Cutaneous diseases often represent spatially heterogeneous and biologically dynamic processes [1, 7]. Tissue sampling is limited, and biopsies capture only a small fraction of the lesional architecture. Molecular alterations may be focal, temporally variable, or present at levels below the detection threshold of routinely applied assays. Furthermore, current molecular techniques interrogate predefined targets; pathogenic mechanisms outside the tested spectrum remain undetected. Negative molecular findings therefore require cautious interpretation. Absence of detection does not equate to absence of disease [1, 3]. Nevertheless, in some diagnostic workflows, molecular results may carry disproportionate weight, particularly when clinicopathological correlation is limited or incomplete. In such settings, morphologically well-supported diagnoses may be questioned or downweighted based solely on molecular negativity, contributing to diagnostic uncertainty [3, 4, 8]. Limited clinical information further amplifies this challenge. In routine practice, molecular testing is frequently initiated with minimal accompanying clinical context [2]. Histopathological assessment may likewise be performed without detailed clinical correlation. When molecular results are interpreted in relative isolation, their limitations may be underestimated, and their impact on diagnostic decision-making may be overemphasized [9]. This undermines the integrative diagnostic approach that has long been central to dermatopathology.

The increasing emphasis on molecularly informed classification schemes adds another layer of complexity. Molecular insights have substantially advanced the understanding of tumor biology and have refined diagnostic categories in many areas of cutaneous pathology. However, defining diagnostic entities primarily

TABLE 1 | Representative examples of discordance between morphological and molecular findings in routine dermatopathology.

Morphological impression	Molecular finding	Diagnostic interpretation	Possible explanantion for discordance
Psoriasiform dermatitis with features suggestive of chronic eczema (e.g., spongiosis, variable acanthosis)	Gene expression profile suggestive of psoriasis	Potential overinterpretation of molecular result; morphology and clinical correlation favor eczematous dermatitis	Overlapping inflammatory signatures; classifier limitations
Classic histopathological features of psoriasis (regular acanthosis, parakeratosis, neutrophils)	Inconclusive or negative psoriasis classifier result	Molecular false-negative or limited sensitivity; morphology remains diagnostically decisive	Sampling error; low inflammatory activity; technical sensitivity limits
Dense plasma cell-rich inflammatory infiltrate suggestive of infectious etiology	Negative molecular assays for common pathogens (e.g., *Treponema pallidum*, *Leishmania* spp.)	Molecular negativity does not exclude infection; sampling limitations and assay scope must be considered	Low pathogen load; focal distribution; limited assay spectrum
Atypical spitzoid melanocytic proliferation with concerning architectural and cytological features	No detectable mutation in commonly associated molecular pathways	Absence of mutation does not exclude entity; classification remains based on morphology and overall context	Genetic heterogeneity; incomplete coverage of relevant pathways
Atypical blue nevus/dermal melanocytic proliferation	No mutation identified within expected molecular spectrum	Molecular findings insufficient for classification; morphology and growth pattern remain central	Undetected or unknown alterations; assay limitations

Note: These scenarios illustrate that molecular results are context-dependent and require careful interpretation within an integrated clinicopathological framework. In situations of discordance, diagnostic resolution relies on the integration of all available data, with histopathological assessment providing the structural and contextual basis upon which molecular findings are interpreted.

by molecular alterations may, in some settings, risk decoupling diagnostic terminology from consistently reproducible morphological patterns. This is particularly relevant in routine diagnostics, where technical, preanalytical, and sampling limitations may prevent reliable detection of defining molecular alterations [7, 10].

These challenges do not reflect shortcomings of molecular pathology itself. On the contrary, molecular diagnostics are indispensable in many areas of dermatopathology. The difficulties arise when expectations exceed the methodological scope of individual assays and when molecular findings are insufficiently integrated into the clinicopathological context. Overinterpretation of negative or discordant molecular results may contribute to diagnostic uncertainty and, in some cases, affect clinical management. Patients present with a pathological process regardless of whether a molecular alteration is detected. Dermatopathology therefore requires a consistently integrative approach. Morphology remains the central diagnostic modality, providing information on tissue architecture and cellular context that cannot be fully captured by molecular techniques. Molecular findings should be interpreted as complementary data that support and refine, but do not independently determine, the final diagnosis. Clear communication of the scope and limitations of molecular testing is essential. Negative results should be interpreted cautiously and always in conjunction with histopathological and clinical findings. Close interdisciplinary collaboration remains critical for meaningful diagnostic integration.

In conclusion, discordance between morphology and molecular findings is a predictable and informative phenomenon in dermatopathology. Recognizing and addressing such discrepancies is essential to avoid diagnostic oversimplification. Molecular pathology is a powerful and indispensable tool, but it does not replace histopathological expertise or clinical judgment. Maintaining morphology as the central integrative element of dermatopathologic diagnosis remains essential for ensuring diagnostic accuracy and clinical relevance in an era of rapidly expanding molecular technologies.

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Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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