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Histopathology of Erythema Nodosum Leprosum With Emphasis on Post-multidrug Therapy Considerations: A Narrative Review

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Abstract

Erythema nodosum leprosum (ENL) (or type 2 reaction) is an immune-mediated complication of borderline lepromatous and lepromatous leprosy. It can appear before treatment, during multidrug therapy (MDT), and in some patients long after MDT has ended. In the dermatology outpatient clinic, a post-MDT patient with tender nodules and fever raises a real diagnostic problem. The differential includes relapse, reversal reaction, Lucio phenomenon, and unrelated panniculitides or neutrophilic dermatoses, while prior therapy may have altered both the bacillary and the histological picture.

This narrative review summarizes published knowledge on the histopathological spectrum of ENL, the biopsy and staining practice needed to capture it, the way treatment history modifies the findings, and the features that separate ENL from its mimics. The central finding is neutrophilic infiltration of macrophage granulomas, usually with dermal edema, leukocytoclasia, and neutrophilic panniculitis. True vasculitis is inconsistent, and its prominence depends on the age of the lesion. After MDT, foamy histiocytes containing fragmented or granular acid-fast debris may persist. In at least one recent post-MDT series, about half of the biopsies still showed active disease or bacillary persistence, so a reaction after treatment should not be equated with bacteriological cure.

We offer a comparison table of histological differentials and a clinicopathological checklist for reporting. We also identify gaps, notably the scarcity of studies that stratify ENL histology by time since MDT completion.

Categories: Pathology, Dermatology
Keywords: erythema nodosum leprosum, fite-faraco stain, histopathology, leprosy, multidrug therapy, neutrophilic panniculitis, type 2 reaction

Introduction And Background

Leprosy expresses the host's cell-mediated immunity against *Mycobacterium leprae* as a spectrum. The Ridley-Jopling system places patients between polar tuberculoid and polar lepromatous disease, with borderline groups in between, and links clinical, immunological and histological features [1,2]. Within this spectrum, patients with high bacillary loads are prone to erythema nodosum leprosum (ENL), a systemic, antibody- and neutrophil-associated inflammatory episode also called a type 2 reaction.

ENL is common and burdensome. A systematic review of incidence data found ENL in about 4.5% of multibacillary cases and 15.4% of lepromatous cases in field-based studies. The same review reported that episodes often recur, with 39 to 77% of affected patients having more than one episode, and that a high bacterial index is the main risk factor. It also noted that ENL may occur years after antibiotic treatment, with late recurrence reported up to eight years after release from treatment [3]. In a Hyderabad cohort of 481 borderline lepromatous and lepromatous outpatients, ENL prevalence was 24% overall, 49.4% in lepromatous and 9% in borderline lepromatous disease. Borderline lepromatous patients with a bacterial index of 4+ or more had higher odds of ENL, and chronic ENL made up 62.5% of cases [4]. A systematic review of immunological studies likewise describes ENL as a painful complication in about 50% of lepromatous and 5 to 10% of borderline lepromatous patients, and notes that the evidence base is hard to compare because of inconsistent case definitions, treatment status, and timing of sampling [5].

That last point matters for pathologists. Histological literature on patients who have already completed multidrug therapy (MDT) is sparse: a dermatopathology article on treated leprosy noted that hardly any literature existed on biopsies from such patients [6]. Yet the post-MDT patient is exactly the one who reaches the dermatology outpatient department with new nodules. Moreover, completing a fixed-duration regimen does not guarantee bacillary clearance. In a Brazilian series of 131 multibacillary patients biopsied after 24 MDT doses, histopathology showed active disease or bacillary persistence in 62 of 123 specimens [7].

This review therefore asks four practical questions. What does ENL look like under the microscope? How should the biopsy be taken and stained so that the answer is not missed? How does prior treatment change

the picture? And how can ENL be separated from relapse, reversal reaction, and other neutrophil-rich or panniculitic conditions? We draw mainly on the histopathological literature, including a retrospective analysis of 64 lepra-reaction biopsies from Mumbai that remains one of the most detailed descriptions of individual ENL features [8].

Review

Review methodology

This is a narrative review, not a systematic review. Sources were identified through targeted web-based searching in October 2026. Bibliographic records were confirmed through PubMed, PubMed Central, publisher pages, and the Infolep leprosy bibliography, and further articles were found by citation chasing from key papers. This was a limited search and was not exhaustive. Search terms combined "erythema nodosum leprosum", "type 2 reaction" and "lepra reaction" with "histopathology", "histology", "panniculitis", "vasculitis", "treated leprosy" and "multidrug therapy". Historical primary descriptions from the 1960s and 1970s were included because they remain the basis of current histological criteria. Every reference cited here was checked against a bibliographic record or the source abstract before inclusion. Where a statement rests on an abstract only, the wording in this review is kept to what the abstract supports.

Pathogenesis relevant to histology

The microscopic picture of ENL follows from its mechanism, so a brief summary helps. In 1969, Wemambu and colleagues proposed that ENL is a clinical expression of an Arthus-type reaction, in which antigen-antibody complexes drive local inflammation [9]. That idea shaped the interpretation of vascular and perivascular changes for decades. A later systematic review of 146 immunological studies, however, concluded that ENL is associated with a neutrophilic infiltrate but that it remains unclear whether the process is truly immune-complex-mediated or whether the complexes are an epiphenomenon [5]. The same review found that raised tumor necrosis factor-alpha and other pro-inflammatory cytokines support a role in the inflammatory phase of ENL, though not necessarily in its initiation, and that increased CD4+/CD8+ ratios have been reported in skin and blood [5].

Gene-expression work in skin lesions gives a mechanistic link to the neutrophil-rich histology. In ENL lesions, a cell-movement program including E-selectin was regulated together with interleukin-1 beta. Toll-like receptor 2 (TLR2) and Fc receptor activation formed part of an integrated pathway for neutrophil migration and inflammation, and thalidomide inhibited this neutrophil recruitment pathway in the experimental system [10]. A review of reaction pathogenesis adds that no laboratory marker for lepra reactions is yet uniformly accepted, which leaves histology and clinical judgment as the working tools [11].

Two practical points follow. First, ENL histology is a snapshot of a dynamic process, so the findings depend on lesion age and treatment. Second, because the underlying driver is antigen load interacting with host response, the bacillary content of the biopsy is part of the diagnostic picture and should be recorded.

Biopsy and specimen handling

The diagnostic clues in ENL sit partly in the deep dermis and subcutis. Neutrophils in subcutaneous tissue were described as an important clue to type 2 reaction in the Mumbai series [8], and a conspicuous neutrophilic infiltrate in the subcutis, with or without vasculitis, is the textbook histological signature of ENL [12]. A superficial shave or a shallow punch can therefore miss the diagnostic compartment. The recommendations that follow reflect common practice and the limits described in the literature; they are recommendations of the review rather than findings from a single trial.

The choice of lesion and the depth of the biopsy come first. A recent, tender nodule should be sampled, because older lesions show sparser neutrophils and more mononuclear cells [8], and when several lesions of different ages exist, sampling more than one stage is informative. An incisional or deep punch biopsy that includes fat is needed to reach the subcutis, so that both lobular and septal compartments can be assessed.

Staining and complementary sampling come next. Hematoxylin and eosin should be paired with a Fite-Faraco or modified Ziehl-Neelsen stain. The Mumbai study did not stain routinely for acid-fast bacilli because it considered them unhelpful for diagnosing reactions [8], but in a post-MDT patient bacillary morphology is central, as discussed below. A slit-skin smear taken alongside the biopsy gives the bacterial index and morphology and helps calibrate the biopsy findings.

Finally, the request form and the report need attention. The request form should record the leprosy classification at diagnosis, the dates of MDT, any corticosteroid, thalidomide, or clofazimine exposure, and the interval since treatment ended, because without this information the pathologist cannot interpret a granuloma with fragmented debris. Structured reporting is also helpful: for type 1 reactions, investigators have identified key histological variables and analyzed how pathologists reach a diagnosis [13], and a comparable checklist for ENL is proposed later in this review.

Histopathological features of ENL

The Granulomatous Background

ENL arises on a lepromatous or borderline lepromatous background. In these groups, the infiltrate consists of macrophages with vacuolated cytoplasm, lymphocytes and plasma cells, and acid-fast bacilli are numerous [12]. Ridley's histological classification, which grades the spectrum from tuberculoid to lepromatous disease, provides the reference frame [2]. ENL is then superimposed on this macrophage granuloma rather than replacing it.

Neutrophils as the Defining Cell

The most consistent finding is neutrophilic infiltration of the granuloma. In the retrospective Mumbai analysis of 42 ENL biopsies, neutrophils within the granuloma were present in every case. Leukocytoclasia and papillary dermal edema each occurred in 81%, and neutrophilic panniculitis in 69% [8]. The authors concluded that neutrophil infiltration of macrophage granulomas is a reliable sign of ENL [8]. In ordinary, non-reactional leprosy lesions, neutrophils are not expected, which is why their presence is informative [8]. Neutrophils were also noted in the interstitium, encroaching on the epidermis and sweat ducts in some sections, and neutrophilic spongiosis was more common than frank intraepidermal pustules [8].

Panniculitis

Subcutaneous involvement is a core feature. The Mumbai series found lobular panniculitis more often than septal or mixed patterns [8]. This contrasts with classic erythema nodosum, which is a mostly septal panniculitis [14], and is one of the architectural points that helps separate the two (see the differential diagnosis section).

Variable Role of Vasculitis

The vascular component of ENL has been argued about for decades. Earlier clinicopathological studies by Job and colleagues in 1964 [15], and by Mabalay and colleagues in 1965, reported vasculitis involving arterioles and venules in roughly half of type 2 reactions, as summarized in the Mumbai analysis [8]. The Mumbai study itself found classical features less often: fibrin in the vessel wall or granuloma in 38% and fibrin thrombi in the vessel wall in only 12%. Its authors concluded that classical signs of vasculitis are not always present in ENL [8]. They also pointed out that the histological expression of vasculitis depends on lesion age, with early lesions showing more neutrophils and fibrin, and older lesions showing more mononuclear cells [8]. Earlier studies, such as the Indian histopathological comparison of type 1 and type 2 reactions [16], often recorded vasculitis as present or absent without itemizing leukocytoclasia, fibrin, or thrombi [8]. Different thresholds for calling vasculitis therefore probably explain much of the discrepancy between series.

The practical message is that a pathologist should describe each component (neutrophils in vessel walls, leukocytoclasia, fibrin, thrombi) rather than relying on a single label, and should not exclude ENL simply because a vasculitis is not obvious. Necrosis and ulceration are fairly uncommon in ENL, in contrast to Lucio phenomenon [8].

Bacilli and Lipid-Rich Macrophages

In untreated or early-treated ENL, foamy macrophages hold large numbers of acid-fast bacilli [12]. A histochemical study of ENL skin biopsies from 14 lepromatous patients found that periodic acid-Schiff-positive diastase-resistant material, acid mucopolysaccharide, neutral fat, phospholipid, arylsulfatase, and acid phosphatase were present around reactional sites but slight or absent within areas of acute inflammation. The authors interpreted this as solubilization and leakage of hydrolytic enzymes into surrounding tissue and suggested a role for lysosomal enzymes [17]. This is of mainly historical and mechanistic interest, but it shows how lysosomal damage was once linked to the lesion.

Discrepancy Between Clinical and Histological Diagnosis

Clinical ENL and histological ENL do not always agree. A study that classified ENL by acute-phase proteins reported discrepancies between clinical and histological diagnosis [18]. The Mumbai authors similarly noted that lepra reactions are not always diagnosable under the microscope [8]. A biopsy that fails to show neutrophils does not exclude a clinical reaction, particularly if the patient has already received corticosteroids or if the lesion is old.

Extracutaneous Histology

ENL is a systemic disease. Lymph nodes from 12 ENL patients showed near-complete replacement by lepromatous granuloma with considerable polymorph infiltration and numerous bacilli, and the authors

proposed an intense inflammatory response followed by avascular aseptic necrosis [19]. A case report described lepromatous leprosy presenting with polyarthritis, myositis, and immune-complex glomerulonephritis, with the authors arguing that the term ENL is inadequate for such multisystem immune-complex disease [20]. Ocular ENL has also been examined histologically and by immunohistochemistry [21]. These reports are a reminder that a skin biopsy shows only one compartment of the reaction.

Post-MDT considerations

Why the Post-MDT Biopsy Is Different

Finishing MDT does not reset the histology. Joshi's descriptive work on treated leprosy showed that biopsies from patients who completed MDT may be "histologically active", meaning diagnostic of leprosy, or "histologically inactive", meaning non-diagnostic findings that suggest regression [6]. In multibacillary disease, macrophages may remain in large numbers after MDT. They become uniformly foamy and, on Fite-Faraco staining, contain fragmented and granular acid-fast debris rather than solid bacilli. Such granulomas persist, and the lesion is still regarded as histologically active even though treatment has been given [6]. A pathologist who expects the dense solid-staining bacilli of untreated lepromatous leprosy may misread such a specimen.

Persistence Is Common in Some Cohorts

A recent retrospective series from a hyperendemic Brazilian setting biopsied 131 multibacillary patients after 24 monthly MDT doses. Histopathology revealed active disease or bacillary persistence in 62 of 123 specimens (about 50%). Quantitative polymerase chain reaction (qPCR) detected *M. leprae* DNA in 96 of 101 patients, and mouse inoculation yielded viable bacilli in 29 of 45 inoculations. The authors recommended post-treatment histopathological, molecular, and inoculation assessment, particularly in patients with persistent reactions or neurological complaints [7]. Three cautions apply. First, qPCR positivity shows DNA, not viability. Second, the inoculation subset was small. Third, the series comes from one region and was retrospective, so the proportions should not be generalized to every setting.

Implications for ENL After MDT

ENL after MDT is plausible on both mechanistic and epidemiological grounds. ENL can occur years after antibiotic treatment, with late recurrence reported up to eight years after release from treatment [3], and persistent bacillary material can continue to act as antigen. It follows that a post-MDT ENL biopsy may show the usual neutrophil-rich reaction superimposed on a granuloma whose bacilli are fragmented or granular. It may also show a reaction on a granuloma that still contains intact bacilli, which raises the question of relapse or treatment failure rather than a simple reaction to dead antigen.

A second effect is pharmacological. Corticosteroids and thalidomide are the usual treatments for ENL, and the histological effect of these drugs is not well characterized in the sources reviewed here. One would expect a long course of immunosuppression to reduce neutrophils, so a negative biopsy in a heavily treated patient should be interpreted against the clinical picture. This is a reasoned expectation, not a documented finding, and it is flagged as a gap below.

Pitfalls Specific to Treated Lesions

Treated lesions can show epidermotropic lymphocytes, and awareness of this helps prevent over-diagnosis of mycosis fungoides [22]. Certain morphological changes in the absence of granulomas have also been proposed as clues that a lesion is inactive after therapy [22]. These observations support a cautious approach: a post-MDT biopsy should be read with the full treatment history in hand.

Differential diagnosis and histological mimics

Table *1* summarizes how ENL differs histologically from its main mimics in a patient who has completed MDT. The key distinctions are explained below.

Condition	Dominant cell and location	Panniculitis/vessels	Bacilli	Key discriminator	References
ENL	Neutrophils within and around macrophage granuloma; dermis and subcutis	Neutrophilic panniculitis, often lobular; vasculitis variable	Foamy macrophages with bacilli; fragmented or granular after MDT	Neutrophils inside granulomas	[6,8,12]
Type 1 reaction	Lymphocytes within granuloma; edema	Lymphocytic panniculitis in some; neutrophils not expected	Variable with position on the spectrum	Edema plus giant cells, no neutrophils	[8,12]
Relapse or persistent disease	Active macrophage or epithelioid granulomas	Not neutrophil-driven by itself	Intact, solid-staining bacilli	Bacillary morphology and bacterial index	[6,7]
Lucio phenomenon	Vessel-centered necrosis in diffuse non-nodular lepromatous leprosy	Necrotizing vasculitis of superficial vessels; mid-dermal endothelial proliferation	Many bacilli in endothelial cells	Epidermal necrosis, endothelial bacilli	[23,24]
Classic erythema nodosum	Septal inflammation; neutrophils early, lymphocytes and giants late	Septal panniculitis, no vasculitis; Miescher granulomas	Absent	Septal pattern, no leprosy granuloma	[14,25]
Sweet syndrome	Dense mature neutrophils, upper dermis	No leukocytoclastic vasculitis in criteria	Absent	Neutrophils without macrophage granuloma	[26]

TABLE 1: Histological comparison of ENL and its principal mimics

ENL: erythema nodosum leprosum; MDT: multidrug therapy

Type 1 (Reversal) Reaction

Edema inside and outside the granulomas, together with large giant cells, characterizes type 1 reactions [12]. In the Mumbai series, the most consistent findings were papillary dermal edema, lymphocyte pyknosis, and intragranuloma edema, and neutrophils are not part of the usual picture [8]. Distinguishing upgrading from downgrading reactions can require serial biopsies [8]. The decisive difference from ENL is therefore the cell type: lymphocytes and edema in type 1, neutrophils in type 2.

Relapse or Persistent Disease

Histology cannot be separated cleanly from clinical context here. The "active" versus "inactive" framework for treated leprosy [6] and evidence of bacillary persistence after MDT [7] mean that granulomas with intact, solid-staining bacilli should prompt consideration of relapse or inadequate treatment, and not simply a reaction to residual antigen. A reaction and relapse can also be hard to separate. This judgment rests on bacillary morphology and bacterial index, and needs clinical correlation, so the review treats it as an interpretive guide and not a validated cut-off.

Lucio Phenomenon

This is a distinct vasculonecrotic syndrome of diffuse non-nodular lepromatous leprosy. A comparative histological study of 11 patients with Lucio phenomenon and 12 with ENL showed that Lucio's reaction is distinguished by epidermal necrosis, necrotizing vasculitis in the walls of superficial vessels, and severe focal endothelial proliferation in mid-dermal vessels, with many acid-fast bacilli inside endothelial cells [23]. Clinically, it lacks the fever, leukocytosis, and tenderness of ENL and does not respond to thalidomide [24]. Necrosis and ulceration are fairly uncommon in ENL [8]. Clinical context therefore remains essential whenever necrotic lesions are present.

Classic Erythema Nodosum

This is mostly a septal panniculitis without vasculitis, with early lesions showing edema, hemorrhage, and neutrophils, and late lesions showing fibrosis, granulation tissue, lymphocytes, and giant cells; Miescher radial granulomas are a recognized histological hallmark [14,25]. It has many triggers, including infections,

sarcoidosis, drugs, and malignancy [14]. A neutrophil-rich septal panniculitis without granulomatous bacillary infiltrate in a post-MDT patient may therefore be unrelated erythema nodosum, but the biopsy must be examined carefully, with acid-fast staining, before leprosy is set aside.

Sweet Syndrome

Sweet syndrome presents with fever, neutrophilia, and tender erythematous lesions, with a diffuse infiltrate of mature neutrophils typically in the upper dermis and no leukocytoclastic vasculitis in its diagnostic criteria [26]. It occurs in classical, malignancy-associated, and drug-induced forms [26]. The absence of a macrophage granuloma with bacilli, and a different depth of infiltrate, distinguish it from ENL, but a patient with known leprosy needs both considered.

Ancillary tests

Ancillary methods are most useful in the post-MDT patient, when morphology alone may not settle whether bacilli are active.

Acid-Fast Staining and Smear

Fite-Faraco or modified Ziehl-Neelsen staining on the biopsy, with a slit-skin smear read for bacterial index and bacillary morphology, is the first and cheapest step. Intact, solid-staining bacilli favor active disease, whereas granular or fragmented forms favor degraded material, as the treated-leprosy literature describes [6].

Real-Time Polymerase Chain Reaction

A TaqMan assay targeting the repetitive element RLEP can detect about 10 femtograms of *M. leprae* DNA, equivalent to roughly 300 bacteria in infected tissue, and correlated closely with microscopic counts (r = 0.98) in experimental tissues [27]. DNA detection is highly sensitive but does not show viability. Reverse-transcriptase assays that measure 16S rRNA relative to RLEP were developed to estimate viability and may be useful to monitor treatment efficacy in biopsy specimens. In eight multibacillary biopsies before MDT, viability fell during treatment [28]. In the Brazilian post-MDT series, qPCR was positive in 96 of 101 patients, which illustrates why DNA positivity cannot by itself diagnose failure [7]. These assays are research or reference-laboratory tools in most settings.

Immunopathology and Gene Expression

Immunohistochemistry has been applied to ocular ENL tissue [21], and skin gene-expression profiling has linked TLR2, Fc receptor signaling, and E-selectin to neutrophil recruitment [10]. Immune complexes have been studied extensively, but their role remains unresolved, and the evidence is hard to compare across studies [5]. For routine practice, neither complement or immunoglobulin deposition nor cytokine staining should be used alone to confirm ENL.

Mouse Inoculation

Inoculation can show viable bacilli, as in the Brazilian series [7], but it is slow and is not a routine outpatient test.

Clinicopathological correlation and diagnostic pitfalls

Histology supports the diagnosis of ENL but does not replace the clinical assessment. The clinical picture of crops of tender erythematous nodules with fever and malaise, often with neuritis or other organ involvement, remains the anchor. Severity can be recorded with the ENLIST ENL Severity Scale, which was validated in an international multicenter study [29]. Pairing a standardized clinical score with a structured histology report lets later studies compare like with like, which is one of the gaps identified in the immunological literature [5].

Proposed Reporting Checklist

Table *2* is the authors' proposal, assembled from the features that the cited studies found informative. It has not been validated and should be treated as a starting point for audit or a prospective study.

Domain	What to record	Why it matters
Request data	Leprosy type at diagnosis, MDT dates, steroid or thalidomide exposure, interval since MDT	Treatment changes bacillary morphology [6]; any steroid effect on neutrophils is presumed, not documented
Specimen adequacy	Depth reached; subcutis present; lesion age	Neutrophils in the subcutis are a key clue; old lesions are mononuclear [8]
Neutrophils	Within granulomas, interstitial, in epidermis or adnexa; density	Neutrophils within granulomas were the most reliable sign in one series [8]
Dermal changes	Papillary dermal edema; leukocytoclasia	Common and supportive [8]
Panniculitis	Lobular, septal or mixed; neutrophilic or lymphocytic	Pattern helps separate ENL, type 1 reaction and erythema nodosum [8,14]
Vessels	Fibrin, thrombi, neutrophils in walls, endothelial proliferation, necrosis	Variable in ENL; necrosis and endothelial changes point toward Lucio phenomenon [8,23]
Macrophages and bacilli	Foamy or vacuolated; Fite-Faraco result; solid versus fragmented or granular; bacterial index	Distinguishes active disease from residual debris [6,7]
Spectrum	Ridley-Jopling group, if assignable	Frames reaction risk and interpretation [1,2]
Comment	Statement of consistency with ENL, relapse, type 1 reaction or other	Links histology back to the clinical question

TABLE 2: Proposed histopathology reporting checklist for suspected ENL in a post-MDT patient

ENL: erythema nodosum leprosum; MDT: multidrug therapy

Diagnostic Pitfalls

Several pitfalls deserve emphasis. Superficial sampling that omits the subcutis can miss neutrophilic panniculitis [8], and waiting for vasculitis is a related error, because classical vasculitis was not present in most ENL lesions in the Mumbai series and its absence therefore does not exclude ENL [8]. A reaction after MDT should not be assumed to reflect dead antigen alone, since post-treatment biopsies in one series showed active disease or bacillary persistence in about half of specimens [7]. Epidermotropic lymphocytes can occur in treated lesions, and mistaking them for lymphoma is another risk [22]. Finally, in late or steroid-treated lesions, a negative biopsy does not rule out a clinical reaction, and the clinical-histological mismatch reported previously reflects this limitation [18].

Gaps in evidence and future directions

Several gaps limit what can be said with confidence about ENL histology after MDT. The most important is that no ENL-specific post-MDT histology series was identified. The post-treatment literature found here describes treated leprosy broadly [6,7,22], and the ENL histology series reviewed here do not clearly report findings by time since MDT [8]. Studies that stratify ENL biopsies by time since MDT completion were not identified in this limited search.

A second gap concerns the absence of agreed histological criteria. For type 1 reactions, key variables have been formally examined [13], whereas for ENL the published series differ in how they define vasculitis, which complicates comparison [8,15]. The role of immune complexes also remains unclear, because the immunological evidence is hard to compare owing to inconsistent case definitions, treatment status, and sampling times [5]. The effect of ENL drugs on histology is likewise unknown, since corticosteroid and thalidomide effects on the neutrophilic infiltrate are not characterized in the sources reviewed.

Practical and epidemiological limitations add to these gaps. Molecular viability methods exist [28] but are confined to research and reference settings and are not routine, and accurate global and regional ENL incidence data are lacking [3].

A useful next step would be a multicenter prospective cohort of post-MDT patients with suspected ENL. Each patient would have a standardized deep biopsy read against a shared checklist (Table *2*), a documented clinical severity score [29], bacterial index and morphology, and molecular assessment of bacillary load and, where available, viability. Follow-up would then show how histology relates to relapse, chronic ENL and steroid dependence.

Conclusions

ENL remains a clinicopathological diagnosis. Its histological core is neutrophilic infiltration of a macrophage granuloma with dermal edema, leukocytoclasia and often a lobular neutrophilic panniculitis, whereas true vasculitis is inconsistent and depends on lesion age. In patients who have completed MDT, histology must be interpreted with treatment history and bacillary morphology, because fragmented or granular debris is expected and intact bacilli suggest ongoing disease. A biopsy that reaches the subcutis, an acid-fast stain, and a structured report allow the pathologist to separate ENL from type 1 reaction, relapse, Lucio phenomenon, erythema nodosum, and Sweet syndrome. The comparison table and checklist offered here are intended as practical aids and as hypotheses for validation, not as validated criteria.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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