Perspective

Limitations of histopathology in diagnosis and management of patients with leprosy

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Diagnosis of patients with leprosy in public health programs is based mainly on clinical findings supplemented by slit skin smear examinations, wherever facilities exist. Skin biopsy plays a very small role in such settings and current WHO/NLEP guidelines have almost no role for histopathologic findings in the management of leprosy.

In practice, however, histopathology plays an important role in the management of a large number of patients with leprosy who present to dermatologists in private practice or to dermatology departments in tertiary care centers and medical colleges, where skin biopsy is often taken and the histopathology findings greatly help the clinician in managing the patient with leprosy.

It is known that macular lesions may be seen throughout the clinical spectrum of leprosy and it is difficult to correlate their clinical, bacteriological and histological parameters.[1] Also a significant clinico-pathological discordance may be seen in borderline (BT, BB, BL) leprosy as compared to polar forms.

In some patients skin biopsies may have findings that are non-diagnostic or have findings that confuse and bemuse the clinician.

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This essay highlights clinical situations where histopathology may be inadequate or confusing and clinico-pathologic considerations play an important role in the management of such patients.

1. *Non-specific findings*: Normal looking skin or sections with just a sparse perivascular lymphocytic infiltrate wherein no specific histologic diagnosis can be rendered may be seen sometimes in indeterminate leprosy, in maculo-anesthetic lesions of leprosy, from areas of sensory loss in clinically normal looking skin in pure neural leprosy and in persistent or new lesions in patients with leprosy that have received adequate multidrug therapy.

2. *Indeterminate histology*: It is difficult to categorically diagnose leprosy in the absence of granulomas and some cases present with "indeterminate" histology wherein leprosy can be diagnosed on clinical findings but no granulomas are seen histologically.

Indeterminate histology refers to selective infiltration by lymphocytes in superficial and deep perivascular, peri-adnexal (eccrine, arrectores pilorum, hair follicles) and peri-neural locations without granulomas. All the above sites are not always involved in a given section and the degree of specificity for suspecting leprosy is in the following order: nerve infiltration is the most specific, followed by infiltration of arrectores pilorum muscles and lastly eccrine glands and ducts. Finding of acid-fast bacilli (AFB) by Fite Faraco stain is helpful but more often than not, bacilli are not seen in pauci-bacillary cases and histo-pathologic findings need to be correlated with the clinical picture.

Indeterminate or non-diagnostic histology is typical of clinically indeterminate leprosy but may also be seen in maculo-anesthetic lesions, some cases of borderline tuberculoid (BT) leprosy and in patients with treated leprosy especially in macular lesions that develop after completion of MDT.

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3. *Reactions in leprosy*: Type 1 reactions occur early in the course of the disease due to immunological alterations in borderline leprosy and present clinically with erythema and edema of existing skin lesions and often with neuritis. Histological correlates that are suggestive of type 1 reactions include dermal edema, inter-cellular edema in granulomas, necrosis in the center of granulomas, apoptosis of lymphocytes and presence of multiple, large giant cells.[2] While the clinical recognition of type 1 reactions is easy, histological concordance is not always seen and in this issue of the journal, Patnaik *et al*.[3] have reported on their study of evaluation of key histologic variables in skin biopsies of borderline leprosy patients presenting clinically with type 1 reactions. They found histologic findings of type 1 reaction in only 67.5% (27/40) patients with clinical features of reaction but on the other hand found features of reaction in 20% (10/50) of patients who had no clinical findings suggestive of a reaction.

Borderline leprosy is immunologically unstable and constant changes in local cell-mediated immunity may be occurring even in untreated cases. Upgrading reactions seen after beginning multidrug therapy (MDT) are characterized by the influx of lymphocytes and development of large giant cells with dermal and intercellular edema whereas downgrading of immunity toward the lepromatous pole results in change of morphology of histiocytes from epithelioid to histiocytic macrophages with foamy and vacuolated cytoplasm.

The finding of histological features suggestive of reaction in patients who clinically do not exhibit signs of reaction may be explained by the time lag that occurs between immunological shifts and the corresponding histological and clinical findings. Clinical changes occur much later than the tissue changes that are reflected in the histopathology.

This however does not explain why some biopsies from patients clinically diagnosed with reactions do not show the expected histological findings indicating a reaction.

Type 2 reactions (ENL) on the other hand may develop long after the recommended course of treatment has been completed and are characterized by collections of foamy histiocytes with infiltration of neutrophils. Vasculitis and panniculitis may be seen occasionally but are not requisites for the diagnosis.

Patients with recurrent erythema nodosum leprosum sometimes show on histology a very banal picture with very few foamy histiocytes and scatter of occasional neutrophils. Such biopsies do not correlate with the florid clinical picture that the patient presents with and may cause confusion if the clinician and pathologist are not aware of this possibility.

4. *Reaction vs Relapse*: Relapse is easy to detect if solid staining bacilli can be demonstrated in slit skin smears or in tissue but in paucibacillary cases, particularly borderline tuberculoid (BT) leprosy, it is very difficult to differentiate between reaction and relapse on histology as bacilli may not be seen. If an earlier pre-treatment biopsy is available for comparison then change of morphology of the granuloma may be a pointer to differentiate between an upgrading reaction and relapse, with macrophages appearing in relapse vs giant cells in reactions.

5. *Evaluation of treated leprosy:* Many patients show persistent skin lesions after completion of anti-leprosy therapy while some patients develop new lesions. Persistence of granulomas in such lesions in the absence of clinical activity is often a cause of confusion regarding the further management of the patient especially if pre-treatment biopsies are not available for comparison.

New lesions that develop after completion of treatment are usually macular and show an indeterminate histology. Morphological changes in the absence of granulomas in patients of treated leprosy have recently been described and may be used as clues to determine "inactivity" of the disease after completion of therapy.[4]

6. *Unusual findings in suspected leprosy:* A few patients suspected to have leprosy have been described with histological findings of follicular mucinosis which resolved completely with treatment for leprosy.[5,6] Epidermotropic lymphocytes are often seen in leprosy, in active borderline disease, in reactions and in lesions of treated leprosy. Awareness of such findings is important to make a clinic-pathological diagnosis of leprosy and to prevent overdiagnosis of mycosis fungoides.

In conclusion, skin biopsy is helpful in the majority of patients with leprosy, especially if supplemented by good Fite staining. However, there are clinical

situations where histopathology has limitations and both clinicians and pathologists need to be aware of this for better management of patients with leprosy.

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