



# The Relevance of Skin Biopsies in General Internal Medicine: Facts and Myths

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## ABSTRACT

**Introduction:** Non-dermatology medical specialties may refer patients for skin biopsies, searching for a particular diagnosis. However, the diagnostic impact of the skin biopsy is not clearly established. This article aims to assess the indications for, and evaluate the clinical relevance of, skin biopsies in non-dermatology medical specialties.

**Methods:** A questionnaire was sent to 23 non-dermatology specialty departments in a university medical center, requesting a list of indications for skin biopsies, as well as to 10 staff dermatologists to collect the indications of skin biopsies requested by non-dermatology specialties. Once the indications were collected, a literature search was performed to evaluate their clinical value and relevance.

**Results:** Eleven non-dermatology specialties provided a list of skin biopsy indications, to which staff dermatologists added seven more indications. A literature search revealed

evidence-based medicine data for six diseases, that is, amyloidosis, peripheral autonomic neuropathy, Sneddon's syndrome, intravascular lymphoma, sarcoidosis, and chronic graft-versus-host disease. Results were questionable concerning infectious endocarditis, acute graft-versus-host-disease, and the lupus band test. Skin biopsy were not evidenced as useful for the diagnosis of calciphylaxis, systemic scleroderma, Behçet's disease, or hypermobile Ehlers–Danlos syndrome. For the diagnosis of Alport's syndrome, pseudoxanthoma elasticum, and vascular Ehlers–Danlos syndrome, skin biopsy is currently outperformed by genetic analyses. For diagnoses such as Henoch–Schönlein purpura and Sjögren's syndrome, skin biopsy represents an additional item among other diagnostic criteria.

**Conclusion:** The usefulness of skin biopsy as requested by non-dermatology specialties is only evidenced for amyloidosis, peripheral autonomic neuropathy, Sneddon's syndrome, intravascular lymphoma, sarcoidosis, chronic graft-versus-host-disease, Henoch–Schönlein purpura, and Sjögren's syndrome.

**Keywords:** Skin biopsy; Diagnosis; Non-dermatology medical specialties; Diagnostic value; Internal medicine

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### Key Summary Points

The relevance of skin biopsies for non-dermatology specialties remains unsettled for many indications.

After collecting the various indications for skin biopsies in non-dermatology specialties, a review was performed for evidence levels.

The usefulness of a skin biopsy as requested by non-dermatology specialties is evidenced for amyloidosis, peripheral autonomic neuropathy, Sneddon's syndrome, intravascular lymphoma, sarcoidosis, and chronic graft-versus-host-disease.

Skin biopsy is one diagnostic criterion among others in calciphylaxis, Sjögren's syndrome, systemic sclerosis, and Henoch–Schönlein purpura.

The utility of cutaneous biopsies remains controversial in infectious endocarditis and acute graft-versus-host disease (GVHD) as well as lupus band test for the diagnosis of systemic erythematous lupus.

Molecular biology has outperformed the sensitivity and specificity of skin biopsies in vascular Ehlers–Danlos, Alport's syndrome, and pseudoxanthoma elasticum even though skin biopsy remains the fastest and cheaper option.

## INTRODUCTION

A skin biopsy performed under local anesthesia is a simple, safe, reproducible, and minimally invasive tool for sampling skin tissue, leaving only a minimal scar. They are of paramount importance to confirm or to help to achieve a precise diagnosis in dermatology. Aside from standard hematoxylin–eosin histochemical staining, a whole array of complementary

techniques is available for refining or confirming the histological diagnosis, including a series of special histochemical stains, immunohistochemical and immunofluorescence techniques, in situ hybridization, PCR, and genetic analyses.

Several non-dermatology medical and surgical specialties may also request or perform a skin biopsy of normal or diseased skin in the workup of some specific diagnoses. However, the usefulness and the relevance of these skin biopsies in achieving a specific diagnosis are not always clear. First, there is the textbook phenomenon where standard diagnostic procedures are often accepted as they are and copy/pasted to the next edition. Second, as there is no or little financial interest from pharmaceutical companies, it is difficult to obtain funding to verify the truthfulness of these indications.

The purpose of this work was to collect the indications of skin biopsies as requested by non-dermatology specialties and to analyze the currently available literature concerning the evidence of relevance and usefulness.

## METHODS

The non-dermatology medical and surgical specialties potentially requesting skin biopsies of their patients were identified by sending a questionnaire to all 23 medical and surgical departments of the university hospital. The questionnaire asked for which specific diseases a skin biopsy is recommended or should be considered. Two reminders were sent.

Another questionnaire was sent to the ten staff dermatologists of the university dermatology department asking for which diseases patients are referred by other medical or surgical specialties for a skin biopsy.

Once the different indications were collected, a literature search was performed to evaluate the clinical value and relevance of skin biopsies according to different levels of evidence. The consulted database was PubMed with English as language, from 1960 to April 2021. The search terms included the names of the specific disease and were subsequently cross-referenced with the following search terms:

“diagnosis,” “skin biopsy,” “cutaneous sample,” “diagnostic method,” “histology,” “immunohistochemistry,” “in situ hybridization,” “PCR,” and “genetic analysis.”

The selected articles were then classified according to their level of evidence, ranging from 1 to 3 (1, literature proof available; 2, expert-based recommendation without literature support; 3, no proof retrieved in the literature).

No authorization of the ethical committee was required as this work did not involve direct access to patient data.

## RESULTS

Eleven non-dermatology specialties (cardiology, gastroenterology, hematology, nephrology, rheumatology, neurology, general surgery, pneumology, ophthalmology, pediatrics, and physical medicine) reported the following indications for requesting a skin biopsy (Table 1). Gynecology, otorhinolaryngology, emergency medicine, urology, medical oncology, and geriatrics did not reply. Psychiatry, anesthesiology, neurosurgery, stomatology, orthopedic surgery, and esthetic surgery did not report any indication or did not reply.

The returned questionnaires from the dermatologists added seven supplementary indications of requesting a skin biopsy by a non-dermatology specialty (Table 1). The level of evidence is listed as well as whether normal or diseased skin should be biopsied, and how many biopsies should be sampled (Table 1). In addition, when available, alternative diagnostic techniques for skin biopsies are indicated and whether the skin biopsy represents the primary diagnostic tool or is considered an accessory tool for achieving a particular diagnosis (Table 1).

Hereunder we briefly discuss the reported indications.

## DISCUSSION

Hereunder we discuss the different indications collected by the two questionnaire rounds.

### Vascular Ehlers–Danlos

Ehlers–Danlos syndrome (EDS) is a group of connective tissue disorders comprising 13 subtypes characterized in different proportions by joint hypermobility, skin hyperextensibility, and tissue fragility [1]. The vascular subtype is mainly caused by type III collagen mutations [2, 3]. This collagen type is abundant in the skin, blood vessels, and visceral organs. Skin biopsies seem logically more accessible to sample than vascular samples to explore the disease [3–5]. Although some dermatopathologists describe changes on light microscopy and/or electron microscopy examinations, most specialists agree that these modifications are non-specific [5–8]. Currently, skin biopsies can be useful to sample for genetic analysis to screen for COL3A1 mutation [1, 9]. In brief, the final diagnosis of the vascular subtype currently relies on molecular genetic testing performed on blood or skin samples with high sensitivity and specificity rather than on light or electron microscopy [1, 10].

### Hypermobile Ehlers–Danlos Syndrome

Generalized joint hypermobility as well as milder cutaneous involvement characterizes hypermobile Ehlers–Danlos syndrome (hEDS), a heritable connective tissue disorder [11]. Light microscopy may evidence elastopathy. Electron microscopy can reveal variability in the diameter of the fibrils, irregularities of the interfibril spaces, and flower-shaped fibrils [12]. However, most experts agree that all these modifications are nonspecific [9]. Since the genetic basis of hEDS is still unknown, the diagnosis of this subtype remains mainly clinical [13] and is based on the assessment of joint hypermobility using the Beighton score [14] with, unfortunately, a controversial specificity, sensitivity, and a high inter-examiner variability [1]. The identification of the causal gene(s) would provide a genetic diagnostic tool [13]

**Table 1** Summary of indications for a skin biopsy per medical specialties

Medical specialty	Indication for skin biopsy	Recommendation for biopsy: diseased or normal skin (single or multiple samples)	Evidence level	Principal diagnostic versus accessory diagnostic argument	References
Internal medicine					
Cardiology	Vascular ED	N	2	Accessory	[1–10]
	Primary and secondary amyloidosis	N/D (M)	1	Principal	[15–26]
		AGS	1	Accessory	[27–31]
	Pseudoxanthoma elasticum	D	2	Accessory	[32–35]
		D			
	Endocarditis				
Gastroenterology	Primary and secondary amyloidosis	N/D (M)	2	Principal	[15–26]
		AGS			
Hematology	Acute GVHD	D	2	Accessory	[36–46]
	Chronic GVHD	D	1	Accessory/	[36–46]
	Sneddon's syndrome	D (M: 3)	1	principal	[47–56]
		N / D	1	Principal	[57–71]
	Intravascular lymphoma			Principal	
Nephrology	Primary and secondary amyloidosis	N/D (M)	2	Principal	[15–26]
		ASG	1	Accessory	[72–78]
	Alport's syndrome	N	3	NA	[79–86]
		D			
	Calciphylaxis				
Pneumology	Sarcoidosis	N/D	3/1	NA/principal	[103–105]
Rheumatology	Behçet's disease	D	3	NA	[106–109]
	Systemic sclerosis	D	3	Accessory	[110–118]
	Systemic lupus and LED	N	LBT 2	Accessory	[119–131]
		AGS	1	Principal/	[132–139]
		Sjögren's syndrome			Accessory
Surgery					
General surgery	Vascular ED	N	1	Accessory	[1–10]
Other					

**Table 1** continued

Medical specialty	Indication for skin biopsy	Recommendation for biopsy: diseased or normal skin (single or multiple samples)	Evidence level	Principal diagnostic versus accessory diagnostic argument	References
Neurology	Hypermobile ED	N	3	NA	[9–14]
	PAN	N	1	Principal	[87–96]
Ophthalmology	Pseudoxanthoma elasticum	D	1	Accessory	[27–31]
Pediatrics	HSP	D	1	Accessory	[97–102]
Physical medicine	Hypermobile ED	N	3	NA	[9–14]

*HSP* Henoch–Schönlein purpura, *PAN* peripheral autonomic neuropathy, *LED* lupus erythematosus disseminated, *ED* Ehlers–Danlos, *GVHD* graft-versus-host disease, *ASG* accessory salivary glands, *LBT* lupus band test, *D* diseased skin, *N* normal skin, *M* multiple, *NA* not of application

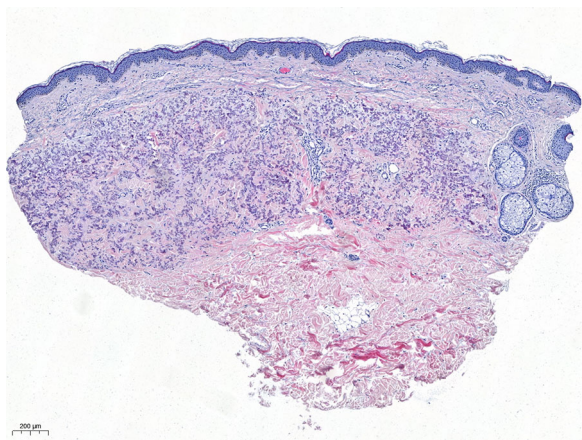
### Primary and Secondary Amyloidosis

Amyloidosis is characterized by extracellular proteolysis-resistant deposits of fibrils leading to the impairment of organ function [15]. Classification distinguishes primary systemic amyloidosis (AL), often associated with myeloma and lymphoproliferative disorders, from secondary systemic amyloidosis (AA), associated with chronic inflammatory conditions [15]. Skin manifestations present as small, smooth, firm, and waxy papules, macroglossia, periorbital purpura, purpuric lesions, and ecchymoses, which are often found in AL amyloidosis but rarely present in AA forms [15]. The diagnosis relies on the recognition of tissular amyloid deposits [16] and is positive when showing Congo red-positive amyloid deposits, with apple-green birefringence using polarized light [17–20]. Immunohistochemistry and/or immunofluorescence with anti-light-chain (LC) antibodies are useful for confirmation [19]. Biopsies of clinically involved organs such as liver, heart, and kidney are highly sensitive but also a lot more invasive [16] than skin samples. The histological examination of cutaneous sample in suspected AA amyloidosis is positive in 50–90% of all cases [17, 19], whereas it is shown to be positive in 50% of all cases in AL amyloidosis [15]. Multiple biopsies are

recommended to increase the sensitivity for diagnosing amyloidosis. Many studies have shown that a salivary gland biopsy is a highly sensitive and specific method for the diagnosis of both forms and is currently considered the gold standard test to diagnose systemic amyloidosis [18, 20–26].

### Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum (PXE) is an autosomal recessive connective tissue disorder characterized by the accumulation of fragmented and mineralized elastic fibers leading to dermatologic, ophthalmologic, and vascular dysfunction [27, 28]. The disease is characterized by yellowish papules or plaque-like skin lesions often appearing in late childhood. The cervical areas are typically involved [27]. A biopsy of lesional skin reveals calcified elastic fibers, narrowed vessel lumen, calcium deposit in the internal elastic lamina, or fibrous thickening of the endothelium (Fig. 1). Therefore, it can be an interesting diagnostic tool [27], whereas a biopsy of clinically normal skin is not useful [29]. Currently, the underlying genetic defect has been identified in the *ABCC6* gene and genetic analysis looking for those mutations are now available with a significantly higher specificity and sensitivity than a skin biopsy of lesional skin



**Fig. 1** Pseudoxanthoma elasticum [hematoxylin–eosin (H&E),  $\times 4$ ]

[28, 30]. Dermatologic examination and skin biopsy used to be the gold standard, but are nowadays replaced by molecular diagnosis [31].

### Infective Endocarditis

Infective endocarditis is a life-threatening disorder that must be rapidly diagnosed and treated to avoid mortality. Osler's nodes and Janeway lesions represent the cutaneous manifestations but are found in only 5–15% of the infected patients. They are highly suggestive of septicemia [32]. Histological findings of both lesions include septic microemboli in small reticular dermal arterioles with the formation of microabscess in the dermis. Leukocytoclastic vasculitis has also been reported but seems not to be specific [32–34]. Microbiological culture may eventually reveal causal microorganisms that can be helpful in the diagnosis. To be more sensitive and specific, skin biopsies have to be performed within 48 h of the onset of the skin lesions [35]. Indeed, the initial skin lesions are later replaced by a nonspecific immunological process. Histology and microbiology can be a prognostic factor, as microabscess formation, visible organisms, and positive bacterial cultures are usually caused by highly virulent organisms [33].

### Acute and Chronic Graft-versus-Host Disease

Graft-versus-host disease (GVHD) is a systemic disease due to allogeneic stem cell transplantation divided into acute and chronic forms, respectively defined as within or after 100 days post-transplantation [36, 37]. Skin biopsies are commonly performed to establish the cause of new skin rashes [38]. Histologic diagnosis of GVHD relies on interface dermatitis, vacuolar degeneration of the basal layer, dyskeratosis, and superficial perivascular infiltrate [37]. However, these alterations are sometimes very subtle and may overlap with other skin diseases of the post-transplantation period, such as drug reactions, viral exanths, and lymphocyte recovery. The usefulness of skin biopsies to confirm an acute GVHD remains controversial in the literature: histological findings are regularly nonspecific, they correlate poorly with the clinical severity of the cutaneous eruption, and they do not allow one to assess the prognosis and progression of a rash [38–41]. In contrast, when chronic GVHD is suspected, a punch biopsy is a valuable tool [42, 43], although diagnosis requires a clear clinic–pathologic correlation. [36, 44]. However, skin biopsy is superfluous if the diagnosis of chronic GVHD has been established by other clinical, biological, or histological criteria [45]. In a consensus paper on performing skin biopsies, 88% of the participants agreed that a skin biopsy is generally indicated in patients with suspected chronic GVHD, whereas only 62% felt that it was necessary in acute GVHD [46]. Unfortunately, only a very small number of studies attempted to evaluate the usefulness of skin biopsies for acute and chronic GVHD.

### Sneddon's Syndrome

Sneddon's syndrome is a rare condition, characterized by a combination of episodes of ischemic cerebrovascular events, caused by antiphospholipid antibody deposits and livedo racemosa. The most striking histological aspects is the occlusion of arterioles by subendothelial proliferation [47–49]. Ultrastructurally, this

thickening corresponds to immigrant medial smooth muscle cells with intermediate filaments colonizing the subendothelial intimal space [47, 50, 51] and shows a positive immunostaining for alpha-smooth muscle actin and tropomyosin [52]. Skin biopsies are often normal, requiring multiple samples [53] to reach a sensitivity up to 80% with three biopsies [47]. The optimal biopsy site is the center of a livedo racemosa ring. In addition, adequate biopsy size and serial sections are required to optimize the detection of a Sneddon's syndrome [47, 54–56].

### Intravascular Lymphoma

Intravascular lymphoma (IVL) is a rare lymphoproliferative disorder characterized by the proliferation of neoplastic B cells, NK/T cells, or monocyte/macrophage variants within the lumina of cutaneous blood vessels, or even as primary dermal presentation [57–60]. Skin lesions observed in about one-third of patients are nonspecific. They mainly appear as erythematous or purpuric nodules and plaques [61, 62]. Diagnosis of IVL involves histopathologic demonstration of neoplastic B or NK/T cells [59]. Since the skin is an easily accessible organ and can show evidence of disease even in apparently healthy skin, cutaneous biopsy must be considered as an important diagnostic tool [59, 63] even without evident skin involvement [61, 62]. However, there are several limitations: studies are rare and have small sample sizes, sometimes with discordant results [63–69]. Sampling precautions must be respected to increase sensitivity. This includes the sampling of normal skin in at least three sites and preferring lesioned skin and angiomas when present [64, 65, 70, 71].

In sum, skin biopsies should always be performed to rule out lymphoproliferative disorder in patients with “unclear” or “therapy-resistant” skin lesions, or in the event of “unclear” fever. Histopathological analysis, immunohistochemistry, and molecular techniques performed on skin biopsies can be crucial for proper classification of hematologic neoplasia involving the

skin and can allow one to stage a lymphoma or a leukemia.

### Alport's Syndrome

Alport's syndrome is a hereditary disorder combining glomerular nephropathy, hearing impairment, and ophthalmologic alterations [72]. It is related to mutations of the type IV collagen and is caused in 85% of cases by *COL4A5* gene mutations on the X chromosome and in 15% by mutations in the *COL4A3* or *COL4A4* genes located on chromosome 2 [72, 73]. Immunohistochemistry on a skin biopsy can identify X-linked Alport's syndrome as the  $\alpha 5$  chain of collagen IV is absent at the dermal–epidermal junction [73, 74]. Hence, immunohistochemistry with specific anti- $\alpha 5$ -chain collagen antibodies does not stain in affected people. The sensitivity exceeds 80%, but its positivity does not exclude the condition and does not permit one to identify the other forms [74–76]. Interestingly, in female carriers, immunostaining of the dermal–epidermal membrane presents a fragmented pattern [73, 74]. Currently, most experts recommend genetic testing for the diagnosis of Alport's syndrome. However, mutation detection is slow, laborious, and expensive whereas the analysis of the skin biopsy is fast, less expensive, and less laborious [77, 78]. In sum, combining clinical data, the family history, and the results of  $\alpha 5$ -chain collagen immunochemical staining on skin biopsies allows one to identify a large proportion of affected patients, hence saving the patient from a renal biopsy and the cost and wait of genetic testing [72, 73].

### Calciophylaxis

The pathogenesis of calciophylaxis, also termed calcific uremic arteriolopathy, an ischemic small-vessel vasculopathy, is multifactorial. Calciophylaxis may occur in patients with renal failure whether dialyzed or not [79, 80] and may present cutaneous ulcerations and/or tissue necrosis [79]. Although the skin lesions are highly characteristic with purplish patches presenting a necrotic center, surrounded by a

painful erythematous edge and indurated subcutaneous nodules especially on fat tissue-rich skin regions [79, 81], the clinical diagnosis remains difficult. The gold-standard diagnostic procedure for calciphylaxis used to be cutaneous biopsy revealing medial and perivascular calcification and intimal proliferation of small arteries. Currently, skin biopsies tend to be avoided as they can lead to chronic and difficult-to-heal ulcerations [80, 81] and present a sensitivity varying widely from 18% to 86% owing to various sampling methods and subjective interpretations of the histopathological samples [82–84]. Furthermore, false negative results can lead to a potentially lethal delay in the treatment [85]. In brief, skin biopsies are only recommended for patients with an uncertain clinical diagnosis. When performed, benefit–risk balance should be carefully evaluated [86].

### Peripheral Autonomic Neuropathy

Peripheral autonomic neuropathy (PAN) comprises a series of disorders characterized by the dysfunction of autonomic nerve fibers [87]. Cutaneous biopsies for the diagnosis of PAN present high sensitivity and specificity, together with the currently available routine autonomic testing [87]. It allows one to characterize and quantify the density of the intraepidermal nerve fibers [88, 89]. Immunohistochemistry using anti-protein-gene-product 9.5 antibodies readily identifies intraepidermal nerve fibers [90–92], adequately distinguishing patients with polyneuropathy from controls [91–95] with a moderate-to-good sensitivity and a high specificity [96].

### Henoch–Schönlein Purpura

Henoch–Schönlein purpura (HSP) is a systemic vasculopathy of the small vessel mainly observed during childhood. HSP presents a nonthrombocytopenic palpable purpura, arthralgia/arthritis, bowel angina, and hematuria/proteinuria. The skin biopsy was not a prerequisite for diagnosis [97] until a large statistical validation process of selected criteria for

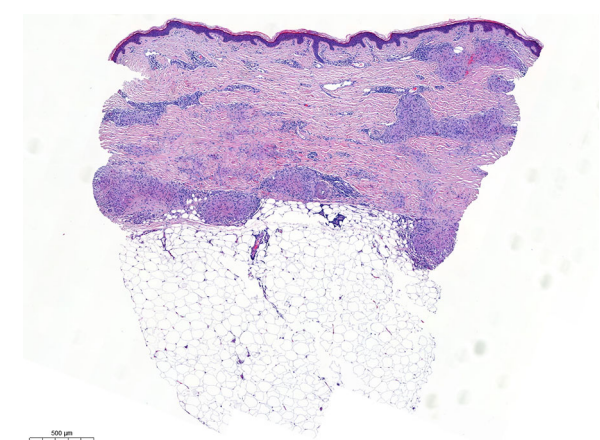
HSP evidenced that predominant IgA deposits on skin biopsy are one of the minor criteria, whereas palpable purpura is the major criterion [98, 99]. Biopsy is also a tool to distinguish HSP from other kinds of purpura especially when performed within the first 24–48 h of the onset of lesions [100]. Hence, skin biopsy is a sensitive criterion but not specific, as vascular deposits of IgA can be retrieved in other vasculitic syndromes [101, 102].

### Sarcoidosis

Sarcoidosis is a multisystemic, inflammatory disease of unknown etiology that is characterized by noncaseating granulomas. The skin manifestations are divided into specific lesions with histopathologically evident noncaseating granulomas and nonspecific lesions that develop as a result of a reactive process [103]. When specific cutaneous lesions are present, a skin biopsy allows an early diagnosis of sarcoidosis through a nonaggressive procedure. The presence of noncaseating granulomas at one site is usually regarded as sufficient for this diagnosis (Fig. 2) [104, 105].

### Behçet's Disease

Behçet's disease is a rare multisystemic vasculitis that affects the skin but also the vascular, neurological, ocular, and articular systems [106, 107]. Mucocutaneous manifestations



**Fig. 2** Sarcoidosis (H&E,  $\times 2.9$ )



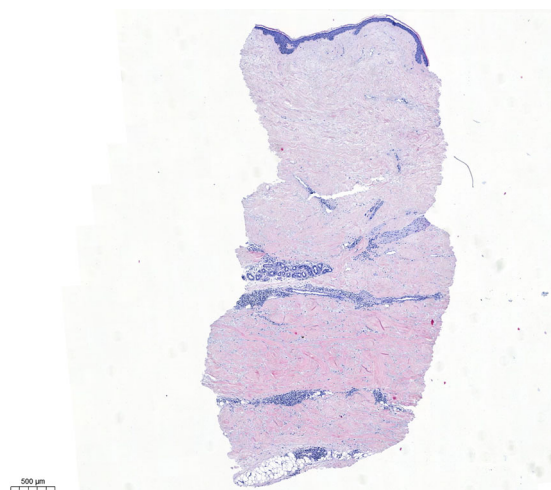
include bipolar (oral and genital) aphthae, which are the most frequent ones, followed by pseudofollicular lesions found in 40–45% of all cases and dermohypodermal nodules present in less than 50% [108]. A skin biopsy is sometimes performed to help establish the diagnosis. However, the histological aspect is nonspecific, revealing polynuclear inflammation with or without arterial obliteration under the necrotic areas. The histological findings are similar in idiopathic aphtous ulcers. Hence, the diagnosis of Behçet's disease is based on a set of criteria, none of them including a skin biopsy [108, 109].

### Systemic Sclerosis

Systemic sclerosis, also known as scleroderma, is a fibrotic process of the skin and various internal organs characterized by three consecutive steps: an inflammatory phase, followed by thickening and finally atrophy of the skin [110]. The histological picture of the skin shows initially microvascular alterations, followed by chronic inflammation evolving toward cutaneous fibrosis and thickening (Fig. 3) [110, 113]. Currently, histological examination does not belong to the diagnostic criteria and is not routinely performed [114]. Skin biopsy is required only in the case of diagnostic doubt with other scleroderma-like disorders or for research purposes [111, 115–118]. The gold standard method to evaluate skin thickness is the modified Rodnan skin score, which should always be correlated with the clinical grounds and autoantibody profile [110, 111]. Changes in the diagnosis criteria could appear in the coming years as recent studies have shown that multiple histologic parameters correlate with severity [116].

### Lupus Band Test in Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with immunological, genetic, and environmental factors, potentially affecting almost any organ. The lupus band test (LBT) compares deposits of immunoglobulins



**Fig. 3** Scleroderma (H&E, ×1.7)

and complements along the dermal–epidermal junction (DEJ) in photo-exposed and photo-protected skin. It is considered positive when one or more immunoreactants (IgG, IgA, IgM, C3) are detected [119, 120]. The interpretation of a positive LBT implies several variables, including the site of the biopsy (lesional or normal skin), the composition of the fluorescent band, the morphology and brightness of the immunofluorescence in conjunction with clinical findings, and serological and immunopathological testing [103–105, 121–123]. The predictive value is greater when C4 (100%), properdin (91.3%), and IgA (86.2%) are identified than with IgM (59%). Furthermore, the specificity and predictive value increase with the number of immunoreactants identified [121, 124–126]. The LBT is positive in about 70–80% of sun-exposed nonlesional skin and in about 55% of sun-protected nonlesional skin in SLE. The LBT used to be considered a sensitive and specific test in the diagnosis of systemic lupus erythematosus, and some authors described it as a prognostic procedure [121, 127, 128], but currently, it is controversial. Indeed, the intensity of the direct immunofluorescence band fails to show any relationship with the degree of inflammation and does not correlate with the level of inflammation in a clinical lesion [129–131].

## Sjögren's Syndrome

Sjögren's syndrome is an autoimmune disease mainly characterized by xerostomia and xerophthalmia due to disruption of epithelial cells and a lymphoplasmocytic infiltration of exocrine glands [132]. Dermatologic manifestations include xerostomia and tumefactions of salivary glands but also xerosis, vasculitis, angular cheilitis, eyelid dermatitis, and annular erythema [133, 134]. The American–European Consensus Group proposed diagnostic criteria among which histopathology and the presence of autoantibodies are the major ones [135]. A positive biopsy is defined as a lymphocytic sialadenitis (FLS) with a focus score of  $\geq 1$  defined as at least 50 mononuclear cells per  $4\text{ mm}^2$  [136]. Minor salivary gland biopsy is a reliable diagnostic tool with an elevated specificity and a sensitivity, ranging from 63.5% to 93.7% [137]. However, diagnostic value of salivary gland biopsy remains unclear owing to circular reasoning in the literature [136], absence of standardized histopathological interpretation and scoring of samples [138, 139], and the need for trained pathologists to perform the reading [139].

## LIMITATIONS

It remains difficult to judge why only 11 out of 23 specialties responded to the questionnaire, either because there is no indication for a skin biopsy in their specialty or because they simply did not respond to the questionnaire despite reminders.

A Delphi consensus-based evaluation of the collected indications involving experts from the different specialties could be a next step of research.

## CONCLUSION

This review aimed to clarify the usefulness of the skin biopsy as diagnostic tool in diseases cared for by non-dermatology specialties.

This review concluded that skin biopsy can be a useful diagnostic tool in amyloidosis,

peripheral autonomic neuropathy, sarcoidosis, Sneddon's syndrome, intravascular lymphoma, and chronic GVHD. Although only a small number of studies evaluated the utility of skin biopsies, all the experts seem to agree.

The utility of cutaneous biopsies remains controversial in infectious endocarditis and acute GVHD as well as the LBT for the diagnosis of systemic erythematous lupus. Current literature supports that a skin biopsy is useless in the diagnosis of Behçet disease and hypermobile Ehlers–Danlos. In calciphylaxis, it used to be a useful tool, but since the benefit–risk balance is not favorable except in highly doubtful cases, it should not be routinely performed. In Henoch–Schönlein purpura, systemic scleroderma, and Sjogren's syndrome, the examination of a skin biopsy represents one additional criterion among many others.

Molecular biology has outperformed the sensitivity and specificity of skin biopsies in multiple indications, including vascular Ehlers–Danlos, Alport's syndrome, and pseudoxanthoma elasticum, even though skin biopsy remains the fastest and a cheaper diagnostic tool. Once the molecular defect of other diseases is determined, skin biopsy will probably become less useful in these indications.

Currently, a lack of strong evidence persists in many indications. Most studies rely on small samples, and the circular reasoning behind these articles is flawed. The field would benefit from further research and a standardized approach to determine the precise role of biopsy in many indications.

However, even when the evidence base is slim, it should also be kept in mind that a skin biopsy remains a quick, inexpensive tool, and is sometimes the only available procedure on site.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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