Chapter 1

Site Selection

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1. Introduction

Skin biopsy is a fundamental method to correct diagnosis in lots of skin diseases. To make a "good use" of it, it is necessary to know at what time, to whom it can be done, how many biopsies, and principally in which sites can be applied.

Once choosing the biopsy site, it must be taken into account several factors that depend on the patient and the type of lesion concerned. Also, it should be considered the elementary type of lesion, the depth of it, and the indemnity of the skin as well as other factors.

Within the type of lesions, there are certain diseases that have special features when the physician decide make biopsy such as pigmented lesions and alopecia.

The skin biospies are extremely useful not only for diagnosis, but also for monitoring, therapy evaluation and sometimes they are the treatment itself for certain skin diseases.

In recent times there have been studies that are used in skin biopsies for the diagnosis and /or follow up of non-dermatological diseases, such as neuropathies and intravascular lymphoma B cells. In these diseases there are not typical or no typical cutaneous lesions. Therefore, it is in these cases when we ask where it would be the most suitable site to take the biopsy.

2. Body

The selection of the site of biopsy depends on two factors which can be classified as: patient-dependent and dependent on the skin lesion.

Among the factors are patient-dependent which we describe as sex, age, skin type and reception of treatments for the condition we are evaluating. Sex and age differences implicate

structural skin and variations in thickness or degree of photoaging, treatments received, such as the use of corticosteroids, may also generate changes. All the above factors are interrelated, since age is inversely proportional to the thickness, broadly photoaging is also associated with age and affects the thickness of the skin, as if the patient is receiving treatment corticoid by parenteral, oral or local cause, a decrease in thickness and increase cutaneous capillary fragility, which could modify the histopathological appearance of skin biopsy.

Besides skin region where the lesion is located is another factor to consider when choosing the biopsy site, as this last point can vary the amount of annexes found, as hair follicles, sebaceous and sweat glands, the presence of previous scars or the presence of inflammatory or reactive changes unrelated to the underlying disease, such as stasis dermatitis in the legs may become evident.

Whenever possible, the operator should take samples from several representative sites on the trunk or proximal extremities, given that skin on the distal lower extremities nearly always shows a degree of inflammatory infiltrate and changes related to superimposed stasis dermatitis; moreover, surgical wounds in distal areas will heal more slowly. [1]

Another more trivial aspect but not less important in some patients, especially in women, is whether the lesion is in a region more or less visible, is not the same to make a skin biopsy in the face or neck than in the abdomen, if it is located on the face or neck it will be convenient to perform the procedure in a way that the possible scar will be the smallest. One shave biopsy is possibly the most likely form of modality used for this area. [2]

Then there are the factors dependent of the skin lesion, first of all, it is essential to select a representative area of the lesion devoid of artefact, it is different taking a biopsy from a tumor than from an ulcer.

With regard to this, when choosing the biopsy site it should be taken into account the type of elementary lesion involved and its evolution time (it depends on the type of lesion, its evolution and the place where the skin biopsy is taken.[3]

For example, in the case of ulcers, biopsy must be performed in the edge of it trying to cover healthy skin, and bottom edge of the ulcer; and in the case of annular lesions, such as granuloma annulare, dermatomycosis, erythema chronicum migrans, erythema annulare centrifugum, cutaneous lupus erythematosus, porokeratosis and others, tissue must be sampled from the active border, in the case of a lump or lesion that is felt more than seen, indicating that it is located in the dermis and / or subcutaneous tissue, it should be done in the deepest part. As shown, each elementary lesion involves certain characteristics that modify the selection of the site from which the biopsy will be taken**. See Table 1.**

A factor to consider at the moment of doing the skin biopsy, is the **level of the lesion in the skin**. In case of lesions located in epidermis and papillary dermis such as melanocytic nevus, age spots, seborrheic keratosis, fibroepithelial polyps, common wart, superficial basal cell carcinoma, melanoma in situ, mycosis fungoides, actinic keratosis, Paget disease (mammary and extramammary), contact dermatitis (allergic and irritant), atopic dermatitis, seborrheic dermatitis, plaque psoriasis, scabies, lichen planus, Gibert pityriasis rosacea and vesiculobullous dermatosis. The skin biopsy should include epidermis and a bit of dermis.

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Disease	Time	Site selection
Alopecia areata	Active	Border
Telogen efluvium	Active	Most hairless
Alopecia scarring	Active	Erythematous, follicular plugs, inflamed follicule
Alopecia paraneoplastica	Suspicious papule	Center
Atopic or contact dermatitis	Acute	Erythematous skin vesicle
	chronic	Lichenified areas
Exanthema	Active	Lesion
Erythema annulare centrifugum	Well-developed lesion	Active border
Erythema multiforme	Targetoid lesion	One from dusky center; one from the erythematous border
Erythema nodosum and all panniculitides	Active lesion, first week	Center
Fascitis	Active	Center
Granuloma annulare	Active	Raised border
Larva migrans	Migrating erythema	Normal skin 2mm above the tip of erythematous line
Lichen planus	Any time	Violaceous papule
Lupus erythematosus discoid	Active lesion	Erythematous scaly plaque with follicular plugs
Lupus tumidus	Active lesion	Anywhere
Lupus erythematosus, subacute cutaneous	Active lesion	Anywhere
Lupus erythematous systemic	Active	Anywhere
Lupus profundus	Depressed center and adjacent area	Center
Mycosis fungoides	1- Patche stage, untreated lesion	1- Center
	2- Plaque stage, non-ulcerated	2- Most infiltrated area
	3- Tumor stage, non-ulcerated	3- Indurated area
Morphea	1- Early	1- Lilac ring
	2- Late	2- Center
Necrobiosis lipoidica	Anytime	Ivory atrophic center, avoid bony area
Nephrogenic fibrosing dermopathy	Sclerotic plaques	Indurated area or sclerotic plaque and normal-appearing skin
1- Parapsoriasis large plaque	1- and 2- any stages	1- Untreated lesion
2- Parapsoriasis small plaque		2- Center
Pityriasis lichenoides chronica	2-3 weeks old	Papulosquamous papule
PLEVA	2-3 weeks old	Necrotic papule
Psoriasis guttate	Late stage	Lesional
Psoriasis plaque	Scaly	Anywhere

Disease	Time	Site selection
Psoriasis pustular	Early pustule	Anywhere
Pyoderma gangrenosum and ulcerative disease	Small, early non-ulcerated lesion	Entire lesion
Scabies	Non-infected	Proximal edge of burrow
Scleromyxedema	Sclerotic skin	Beaded papules
Tinea corporis	Untreated, if possible	Erythematous raised border
Tinea pedis	Untreated, if possible	Vesicular or scaly border
Urticaria and urticarial vasculitis	Active 3 days	Lesional

Table 1. Add caption

If it involves papillary and reticular dermis the technique must include these layers, these lesions are melanocytic nevus, glomus tumor, neurofibroma, hemangioma, sebaceous nevi, follicular cysts, basal cell carcinoma (solid, sclerodermiform), melanoma, squamous cell carcinoma, photoallergic dermatitis, phototoxic dermatitis, polymorphic light eruption, scleroderma, morphea, scabietic nodules, leukocytoclastic vasculitis, cutaneous lupus erythematosus, urticaria, granuloma annulare.

If they involve reticular dermis and subcutaneous tissue the biopsy has to be deeper, these lesions are blue nevus, lipoma, dermatofibroma, epidermoid or trichilemmal cysts, melanoma, cuteaneous lymphoma, dermatofibrosarcoma protuberans, metastasis (melanoma, breast cancer), panniculitis, sarcoidosis, rheumatoid nodules, nodular vasculitis, polyarteritis nodosa, thrombophlebitis, granuloma annulare. [4]

In skin diseases that manifest with multiple lesions, once the physician performs complete physical examination of the patient along with a complete history he/she will choose the lesion to perform the biopsy. He/she will observe the most recent lesions, the most representative ones, in which no treatment was done, medically indicated or not, and if it is an evidence of more than one type of elementary lesion, he/she will decide to make as number of biopsies as types of lesions are present. If several specimens are obtained from different lesions or appearance of different ages, these should be placed in different and appropriately labelled containers. [3]

In addition, if an **infectious process** is suspected, then part of the tissue should always be submitted for microbiology studies to identify bacteria, mycobacteria, fungi and viruses. [3]

As stated, skin biopsies must contain adequate specimen to include the three basic components of the skin, but this depends on several aspects, a factor taken into account for this to be possible, is the indemnity of lesional and perilesional skin, whether it is friable or soft it is more likely that at the time of the procedure is difficult to show the three layers of the skin in the histopathological examination. If it is hard or fibrous, it is more difficult to accomplish but it is easier to show the various layers of the skin. The ideal lesion to be biopsied is the harmless and / or without signs of infection, it is sometimes difficult to be like this way because in the case of patients with pruritic lesions they can be infected by scratching. For these reasons, it is advisable that before performing skin biopsy, the lesion should be evaluated and if necessary,

prescribe antibiotics or local anti-inflammatories and after these take effect, do the same. It is also common for patients that self-medicate or those who use different free sold medications that modify the appearance of the lesion.

We note that an **untreated lesion** should be selected for biopsy, or in addition, one should discontinue therapy for one week (if possible) before taking the biopsy. [3]

When someone performs a skin biopsy with diagnostic purposes, for therapeutic monitoring or therapeutic evaluation it should not be always done on skin lesions, it can also be done on normal skin, this happens in cases of experimental studies in which healthy skin should be compared with affected skin. Also, biopsy of healthy skin close to skin lesions when you suspected vasculitis or bullous disease such as bullous pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, cicatricial pemphigoid, dermatitis herpetiformis, pemphigus or some kind of non bullous diseases that may present blisters as lupus erythematosus or lichen planus, for direct immunofluorescence seeking deposits of antibody as IgG, IgA, IgM, C3, fibrin, or complexes antibody- antigen. [3][5][6] This assay should be performed in lesions that have less than 24 hours of evolution, since otherwise it is difficult to observe the presence of immunocomplexes and there are only reactive changes. [6]

Certain pathologies involve a careful choosing of the biopsy site, such as pigmented lesions and alopecia.

Excisional biopsy should be performed in pigmented lesions, but in some cases it can´t be done, the most representative area would be selected. [6] The skin biopsy is the fundamental tool of the dermatologist to evaluate the nature of a pigmented lesion. Clinical examination and dermatoscopy are currently the two widely utilized modalities for examination of pigmented lesions. [2]

In a randomized controlled trial, dermatoscopy added to routine physical examination was also shown to decrease the number of biopsies without decreasing the number of melanomas that were detected. [7] There are 3 major techniques for the biopsy of a pigmented lesion: shave biopsy, punch/incisional biopsy, and excisional biopsy. [8]

The decision to biopsy a pigmented lesion rests principally on the clinician's experience; dermoscopy is useful too. When deciding whether to biopsy or not, Bolognia has said that in case of pigmented lessions the first step is visualizing the gross configuration of the tumor as well as a cross-section of the skin that contains the tumor cells. Thus, an important part of the physical examination is palpation of the suspicious lesion. Due to the fact that a melanoma with invasion feels thicker than a melanoma in situ, palpation can aid in the selection of the biopsy method. [8][9]

In case of multiple pigmented lesions the most unusual appearing lesion is the one that must be taken the biopsy. Guidelines of the British Association of Dermatologists indicate that excisional biopsy of clinically suspicious lesions is almost always preferable to any other technique. And they note that each clinical scenario relies on decision making that takes many factors into account.[10]

The American Academy of Dermatology has recently issued a position statement on the management of melanoma, recommending that a narrow excisional biopsy with 1 mm to 3 mm margins is required to clear the subclinical component of most atypical melanocytic lesions and it is therefore preferable in almost all scenarios. [11] When performing a shave biopsy of a pigmented lesion, the best is to remove the diameter of the lesion completely, otherwise the biopsy is considered a partial biopsy and the true nature of the lesion cannot be ascertained with accuracy by the examining pathologist. If a lesion is large and biopsy of the entire area would leave a significant scar, it is better to biopsy the darkest or most unsual part of the lesion. [8] Another remarkable aspect of the shave method is to provide good cosmetic outcome, as we described before.

Incisional biopsies have been recommended in other circumstances, including extensive or large pigmented lesions with unclear margins, extensive facial lentigo maligna, pigmented lesions in acral areas, and pigmented lesions in mucosal areas. [12] Somach et al study found a diagnostic discordance between incisional and excisional biopsy of about 40% in lesions evaluated. This finding indicates that the portion of the lesion most worrisome to a clinician may not correspond to the most histologicaly aggressive portion of a melanocytiv lesion. [13] The disadvantage of the incisional biopsy technique is overcalling the lesion as a melanoma when it is not, [8] or missing the diagnosis of a melanoma.

The gold standard for melanoma diagnosis is excisional biopsy, and it should be performed on any lesion that is highly suspicious for melanoma. One way to select the site or the size of the excisional biopsy is using a Wood's lamp to detect subclinical pigmentation. The orientation is along the relaxed skin tension lines and the draining lymphatics from the site. This orientation theoretically allows a more accurate sentinel lymph node biopsy if it is later needed. On the extremities it is preferable to orient such excisions vertically rather than horizontally to preserve better the lymphatic architecture. [8]

When the decision to biopsy melanonychia is made, there are 3 main methods to do: a 3-mm punch biopsy, a shave biopsy, or a fusiform excision to the periostium. Although the most widely accepted one is a longitudinal full-thickness excisional procedure, given that shave biopsies fail to evaluate the thickness of the lesion. [14] Before obtaining a biopsy, the nail plate is viewed end-on with dermoscopy, because lesions that are present in the dorsal nail plate reflect a melanocytic origin at the proximal nail matrix, whereas lesions presented in the ventral nail plate correspond to origin at the distal nail matrix [2]

Various choices for biopsy are available depending on the presence of Hutchinson´s sign, width and location of the nail band, and the origin within the matrix of the nail band. Regardless of the biopsy type, pain management and control of bleeding are paramount. [2]

When melanoma is highly suspected in a pigmented band, nail biopsy should include as much of the longitudinal band, including periosteum, as possible. Ideally, the proximal nailfold and nail plate should both be reflected to allow visualization of the origin of the melanonychia. For lesions smaller than 3 mm, a telescoping punch biopsy technique can be used. [2]

When the pigmented lesion is in the lips the site selection depends on the location of it. On the cutaneous lip, a shave biopsy is acceptable if the lesion does not cross the vermilion border. [8]

On the mucosal lip, a punch biopsy is preferred. [8] If the pigmented lesion crosses the vermilion border, a punch biopsy should be performed with orientation vertically. The border of the lip should be marked with a gentian violet marking pen so that when the suture is placed to close the defect, the border can be aligned precisely. [8]

Scalp skin biopsies are frequently performed for evaluation of the classification and patogénesis of **alopecias**. Two 4-mm punch biopsy specimens, both submitted in buffered formalin, are required: one for vertical (longitudinal) sections, and the other for transverse (cross) sections. If only one specimen is available, it is bisected vertically, one side (cut side down) for vertical sectioning and the other side sectioned at 1mm below the skin surface, both pieces are embedded with sides cut down for serial sections. [3] There are limitations in interpreting scalp skin biopsies in both vertical and cross sections: biopsy site selection is critical; the histopathologic features of several end-stage alopecias cannot be distinguished and a 4 to 6mm biopsy sample may not be representative of the entire scalp area. [3] In suspected cicatricial alopecia a sample should be sent to histopathology and another one to perform immunofluorescence. [6]. In cicatricial alopecias, mainly cutaneous lupus erythematosus and lichen planus, the biopsy must be performed in an active margin, trying to choose the edge of the activity or scar areas and (ideally no more than one third of the surface area should correspond to scar). [6]

Another factor to consider in choosing the biopsy site is the goal of it, because it could be for diagnosis, monitoring or treatment. In case it is diagnostic, the site selection and depth varies according to the type of elementary lesion concerned, but in most cases the center of the lesion is the chosen place.

When the biopsy is for diagnosis, it always should, regardless of the method that is done, try to cover the three layers of skin: epidermis, dermis and hypodermis. This last layer is essential especially in nodular lesions, more palpable than visible.

Rajaratnam et al revised 100 skin biopsies and in 78% of the cases, histology with the aid of clinical information was able to provide an accurate diagnosis correlating to the working diagnosis. [15]

The skin biopsy has been reported to be of varying usefulness in making a diagnosis. [15][16]

As stated earlier the biopsy site will depend on the type of elementary lession, but in general, incisional biopsy is preferred and will be at the center of the tumor and inflammatory lesions, in the annular rim of annular lesions and shall include center and border in ulcers areas. In the case of pigmented lesions excisional biopsy is preferred.

When a biopsy is performed to follow a disease is suggested to do it in the same place as the biopsy was made to diagnose, not exactly at the same, but as close as you can, because if done in the exact place, only scar tissue will be evident in histopathological examination. Skin biopsy for this purpose is not necessary to do as a routine procedure, but it is indicated when the underlying disease is malignant and treatment of it was just local, it is carried out to assess whether it was successful or not. It can also be used as a tool for non-responsive dermatoses. Another plausible case for the biopsy is when the first diagnosis was basal cell carcinoma or squamous cell carcinoma and in the time of definitive treatment initial lesion can not be found,

a second biopsy was performed at the site of the first or adjacent to it, to make the right treatment.

In most instances, the purpose of the biopsy is diagnostic or monitoring, but often ends up being therapeutic,in spite of the fact that it hasn´t been the main objective. That is, for example, when the lesions are small, that is to say entering in a punch of 6 mm or less. It has also been described in cases of basal cell carcinoma or keratoacanthoma in which after diagnostic biopsy at the time of definitive treatment, is not even the primary lesion biopsied. On these cases a second biopsy must be performed to do the correct treatment. In cases where no lesion was found, the biopsy ended up being therapeutic without being this its first target. [17]

Laboratories in Europe and the USA have increasingly included skin biopsy in the diagnosis assessment or follow-up of patients with **Peripherals neuropathy.** [18] When a skin biopsy is done with this purpose, it can be done at any site of the body. A 3 milimeters diameter punch is commonly used with no need for sutures. For diagnostic purpose, one skin biopsy is commonly done at a distal site on the leg (10 cm above lateral malleolus) and a further biopsy taken at a proximal site on the thigh (20 cm below the iliac spine); thus a proximal site and a distal site can be compared if a length-dependent process is suspected. Skin biopsy can also be done in other regions of the body (eg. Face, trunk, or fingers). [18]

Skin biopsy is a safe, minimally invasive, painless and cheap tool to provide diagnostic information on small nerve fibers, which are invisible to routine neurophysiological tests. Sommer et al in his experience with more than 1000 biopsy samples, he discovered that there were not side-effects or complaints. Healing in those cases was usually complete within one week, and barely visible scar usually remains. [18] Biopsy can be performed in hairy skin to investigate unmyelinated and thinly myelinated fibers and in glabrous skin to examine large myelinated fibers. [19]

One further advantage of skin biopsy over conventional nerve biopsy is that it allows somatic nerve fibers to be distinguished from autonomic nerve fibers. Morphological changes, axonal degeneration and abnormal regeneration occur in cutaneous nerves very early in the course of peripheral neuropathies, making skin biopsy a promising tool to investigate the progression of neuropathy and the effect of neuroprotective treatments in clinical practice and trials.[19]

The neuropathies in which the skin biopsy is useful are diabetic neuropathy [18], demyelinating neuropathies like Charcot-Marie-Tooth disease. [20][21], neuropathy associated with systemic diseases including sarcoidosis, systemic lupus erythematosus, Sjögren's syndrome, celiac disease, and Friedreich's ataxia and Fabry's disease. [22][23][24][25]. Infectious and inflammatory neuropathies like leprosy, HIV-associated sensory neuropathy, Churg Strauss syndrome. [26][27].

In diabetic neuropathy, skin biopsy is the most sensitive measureof a charge in the severity of neuropathy. [18] Monitoring method is an useful to track the progression of neuropathy in trials of neuroprotective treatments. In case of using skin biopsy to monitor progression or evaluate the effect of neuroprotective treatments; it should be repeated close to the site of a previous biopsy, within the territory of the same sensory nerve [19]Another use of blind skin

biopsy is in the diagnosis of **intravascular B-cell lymphoma**. This lymphoma is a rare one and its diagnoses turns really difficult so blind skin biopsy is an option for diagnosis.

Cutaneous manifestations of intravascular large B-cell lymphoma are nonspecific and appear as edema, peau d'orange, nodules, patches, plaques, and/or telangiectasias and can mimic common lesions such as thrombophlebitis, livedo, or vasculitides. [28] These skin lesions are the result of malignant lymphocytes distributed heterogeneously throughout the papillary and reticular dermal vascular plexuses. [28][29].

Le et al describes the use of blind skin biopsy in this type of lymphoma and despite the absence of cutaneous findings, skin biopsy specimens were obtained. There are limited data on how often blind skin biopsy specimens yield positive results in intravascular large B-cell lymphoma, and there are no guidelines on which sites to choose or how many biopsies to perform. [30] One way to select the site of biopsy is reviewing the frequency depending on location, a recent review reported: thigh (41%), leg (35%), trunk (31%), arm (15%), and buttock (7,5%).[28] Based on this review, biopsy specimens from the case of Le et al were taken from the front of the thighs bilaterally, with 3 of the 4 revealing intravascular large B-cell lymphoma. [30] They have done more than one biopsy because of the small size of the biopsy specimen itself. The skin biopsy is a valuable and minimally invasive diagnostic tool that should be considered for patients with a high index of suspicion for intravascular large B-cell lymphoma, even in the abscense of cutaneous findings. [30]

Sjoberg et al described another use of skin biopsy, it can be useful to remove sea urchin spines.

A biopsy punch with a diameter of 2 mm was used to cut out each spine including a small piece of surrounding dermal tissue to support the fragile remmants of calcium carbonate. [31]

Sjoberg et al exposed that a dermal biopsy punch, commonly found in most medical offices, is a simple and handy tool to solve this problem and thereby reducing the morbidity of the patient [31]

In these cases, site selection is exactly where the urchin spine is located.

3. Conclusion

In our search for information on the most suitable biopsy sites and stage of disease for optimal pathologic diagnosis, we did not find any article devoted entirely to this subject. Only sketchy information was available. Skin biopsy is an accessible tool, easy to perform, inexpensive, relatively safe and allows us to access the histopathological examination of the skin in all its depth, all layers, and microbiological studies or immunofluorescence or immunohistochemistry can be made from it. This diagnostic method is for the dermatologist what the blood test is for the clinicians. Notably, its basic use, the most important and widely disseminated is in the diagnosis of various skin diseases, but it can also be used in monitoring and therapeutic evaluation of these diseases. For its easy carrying and accessibility, its application has been described in the diagnosis of non-dermatological diseases such as peripheral neuropathy,

innovative application, which is deployed on multiple research studies, and offers a less invasive and easy –to-perform tool for the diagnosis of this pathology.

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