

Updated Role of High-frequency Ultrasound in Assessing Dermatological Manifestations in Autoimmune Skin Diseases

Ke CHAI^{1,2}, Ruixuan ZHU^{1,2}, Fujian LUO³, Yaqian SHI^{1,2}, Minghui LIU⁴, Yangfan XIAO^{5,6*} and Rong XIAO^{1,2}

¹Department of Dermatology, ²Hunan Key Laboratory of Medical Epigenetics, ⁴Department of Diagnostic Ultrasound, ⁵Clinical Nursing Teaching and Research Section and ⁶Department of Anesthesiology, The Second Xiangya Hospital of Central South University, Changsha and ³Department of Diagnostic Ultrasound, Huichang County People's Hospital, Ganzhou, China

Autoimmune skin diseases are a group of disorders that arise due to the dysregulated immune system attacking self-antigens, causing multiple tissue and organ lesions. With disease progression, the physical and psychological health of patients may be seriously damaged. High-frequency ultrasound is non-invasive, reproducible, and suitable for visualizing the fine structure of external organs. The usage of high-frequency ultrasound has increased in recent years in the auxiliary diagnosis and monitoring of various skin diseases; it serves as a promising tool for dermatological disease assessment. This review summarizes the characteristics of high-frequency ultrasound imaging in common autoimmune skin diseases, including systemic lupus erythematosus, scleroderma, psoriasis, dermatomyositis, and pemphigus/pemphigoid. The objective of this review is to provide new ideas and strategies for dermatologists to diagnose and track the prognosis of autoimmune skin diseases.

Key words: high-frequency ultrasound; autoimmune skin diseases; ultrasonic imaging mechanism; skin pathology.

Accepted Aug 11, 2022; Epub ahead of print Aug 11, 2022

Acta Derm Venereol 2022; 102: adv00765.

DOI: 10.2340/actadv.v102.1969

Corr: Rong Xiao, Department of Dermatology, and Yangfan Xiao, Department of Anesthesiology, The Second Xiangya Hospital of Central South University, Changsha, China. E-mails: xiaorong65@csu.edu.cn; xiaoyangfan@csu.edu.cn

Autoimmune skin diseases are a group of disorders that arise due to the dysregulated immune system attacking self-antigens, causing skin lesions (1). These diseases can also involve other tissues and organs in the body, seriously affecting an individual's health and quality of life. Therefore, early diagnosis, prompt intervention, and regular follow-up of autoimmune skin diseases are essential for improving disease outcomes. Thus, autoimmune skin diseases may be diagnosed based on the patient's clinical manifestations and the results of serum-specific antibodies or histological biopsy (2). However, some of these autoimmune dermatoses lack specific diagnostic antibodies, and the positive findings can also overlap across disorders. Although histological biopsy is generally considered the gold standard, invasive procedures limit its use in early diagnosis and sub-

SIGNIFICANCE

The diagnosis and assessment of autoimmune skin diseases are limited by the lack of non-invasive and reproducible tests. High-frequency ultrasound can provide details for analysing the skin and its appendages. Visualization using high-frequency ultrasound in dermatology is becoming increasingly common. However, these diagnostic and assessment methods have not been summarized and standardized in autoimmune skin diseases, hampering the development of disease control strategies. Reviewing the detailed high-frequency ultrasound findings of autoimmune skin diseases and correlating these ultrasound findings with clinical manifestations and disease pathology will maximize the clinical benefits for patients.

sequent follow-up. High-frequency ultrasound (HFUS) is an emerging technique for the non-invasive diagnosis and management of diseases (3). A higher ultrasound frequency leads to less tissue penetration but better resolution (4). As such, different ultrasound frequencies are selected according to the depth of target tissue and the range of lesions involved (5, 6). Ultrasound with a frequency of 20–25 MHz shows epidermis, dermis, subcutaneous soft tissue, and the junction between them, and it is widely used in dermatology. In bullous dermatoses, in which the superficial details of the epidermis and the dermis need to be examined, ultrasound with a frequency of 50–75 MHz with high resolution is appropriate. However, ultrasound with a frequency of 12–18 MHz with relatively good penetration may be selected to observe dermatomyositis and other skin diseases, where it must be made clear whether there is a combination with deeper lesions in the subcutaneous layer (7). As a promising tool for dermatological disease assessment, HFUS provides details for analysing the skin and its appendages, which makes the auxiliary diagnosis and the monitoring of various skin diseases more convenient (3, 4). This review summarizes the features of HFUS imaging in common autoimmune skin diseases and correlates ultrasound findings with clinical manifestations and disease pathology. The primary aim of this review is to provide additional clues for clinical assessment of dermatological disease in order to maximize the clinical benefits for patients.

ULTRASOUND TECHNOLOGY AND IMAGING MECHANISMS

Two-dimensional ultrasound

When subjected to voltage, the ultrasonic transducer generates acoustic waves, which will propagate in the surrounding structures; the back-waves reflected by these tissues return to the transducer and form a visual image (4). High-frequency equipment has excellent resolution and limited penetration for the observation of superficial structures (8, 9). In normal skin, the density determines the echogenicity of each layer, which can influence the ability of ultrasound waves to pass through the tissue (10). Dense structures reflect a more significant number of waves, resulting in hyperechoic ultrasonographic structures (11). The main components responsible for the echo differences are the keratin in the epidermis, the collagen in the dermis, and the fat lobules in subcutaneous tissue (6). Ultrasound imaging appears hyperechoic when there is the accumulation of keratin and collagen in the skin layer, whereas adipose tissue in the subcutaneous layer usually appears hypoechoic (8).

Colour Doppler flow imaging

Doppler ultrasound processes relatively moving sound waves emitted by the transducer and reflector with autocorrelation techniques (8). Doppler is applied for elucidating moving structures, such as blood flow in the skin and subcutaneous tissue; in this context, the blood flow signals are superimposed on 2-dimensional images by colour-coding to form colour Doppler flow images. On colour Doppler, the blood flow is differentiated by colours, with red representing arteries and blue representing veins (8, 12). Typically, slight blood flow signals could be seen in the skin and subcutaneous tissue. Inflammation causes vascular congestion and expansion and increases flow volume (4).

Ultrasound elastography

Sonoelastography is a relatively new imaging technique based on tissue stiffness. Shear-wave elastography (SWE) techniques use short pulses of ultrasound to generate shear waves, triggering tissue motion (13, 14). B-mode ultrasound calculates the propagation velocity in the corresponding tissue by detecting the tissue displacement caused by the shear wave (14, 15). Shear waves propagate faster in stiffer tissues and slower in softer tissues (16). Therefore, SWE provides a quantitative measure of tissue stiffness, which can be expressed in terms of shear-wave velocity (m/s) or Young's modulus (kPa) calculated using a specific formula (15). SWE is traditionally colour-coded; blue is usually adopted for encoding soft consistency, red indicates hard consistency, and yellow and green encode intermediate stiffness.

ULTRASONOGRAPHY IN AUTOIMMUNE SKIN DISEASES

Scleroderma

Scleroderma is an autoimmune connective tissue disease that can be separated into 2 subtypes: localized scleroderma (LSc) is generally thought to be a skin-limited disease with occasionally extracutaneous tissue involvement; systemic sclerosis (SSc) is characterized by vasculopathy and fibrosis of the pervasive skin and various visceral. Nevertheless, both LSc and SSc share cutaneous fibrosis as a notable feature (17). Scleroderma skin lesions progress through 3 stages: oedema, fibrosis, and atrophy. In the first stage, painless oedema of the hands, lighter skin texture, and thickened skin occur; in the second phase, the lesions progress rapidly, with a waxy sheen on the surface, and the skin becomes stiff and tight, attached to its underlying tissue, making it difficult to pinch. During the final stage, the skin atrophies and becomes thinner, combining with underlying tissues. The following pathological manifestations are closely associated with clinical stage (18, 19): (i) the oedematous phase, which is characterized by tissue swelling, inflammatory cell infiltration, with less collagen deposition; (ii) the sclerotic phase, which is marked dermal thickening with increased and disorganized dermal and subcutaneous collagen deposits, vessel wall thickening, and luminal narrowing; (iii) the atrophic phase, in which the cortical thickness decreases, the vascular lumen narrows (stenosis) or is blocked (occlusion), skin appendages disappear, and collagen deposits are arranged in dense cell bundles.

The application of ultrasound in scleroderma is gradually refined, and the manifestations are clinically and pathologically relevant. Li et al. (20) reported that HFUS could measure skin thickness quantitatively, proving that skin thickness correlates with a valid measure of SSc activity, and have identified the minimal detectable difference. HFUS can evaluate the activity of the disease. Wortsman et al. (21) found that ultrasound diagnosis sensitivity and specificity are 100% and 98.8%, respectively, compared with the gold-standard histological findings. An exploratory study (22) detected significantly higher skin elasticity and viscosity values in patients with SSc than in healthy controls using HFUS. Meanwhile, Zhang et al. (14) found that the skin elasticity and the surface wave velocity of patients with SSc positively correlate with the modified Rodnan skin score, while there is no correlation between skin viscosity and the modified Rodnan skin score. The author of this article previously conducted an exploratory study of ultrasound manifestations in scleroderma (all lesions were compared with peripheral or contralateral normal skin) and summarized it as follows (23, 24): in the oedematous phase, there were dermal thickening and a reduction in echogenicity of the skin, without apparent changes in the

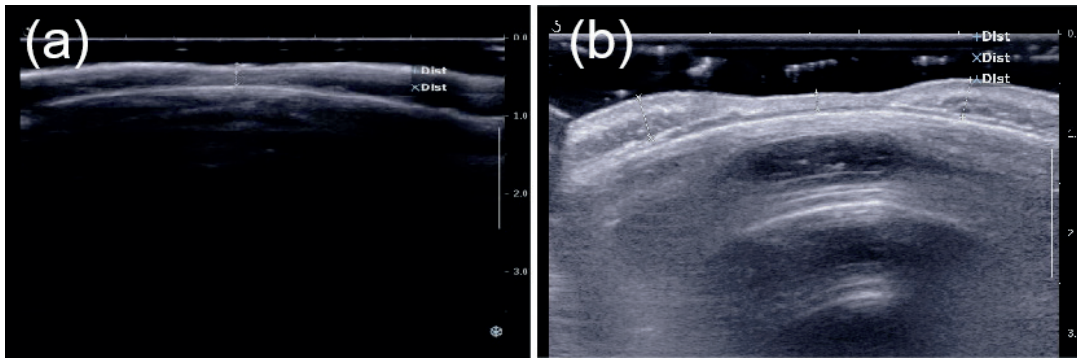


Fig. 1. (a) In the sclerotic phase, the thickness of the cutaneous layer and subcutaneous layer in systemic scleroderma lesions is decreased slightly compared with the surrounding normal skin, and the echogenicity is higher. (b) Atrophic phase: the skin is atrophic and sunken, the subcutaneous fat layer disappears, and the echo increases.

subcutaneous layer, probably because of inflammatory exudation from the lesion, as well as increased fluid in the skin, resulting in swelling and thickening. Meanwhile, the skin elasticity was mildly elevated, and the blood flow signal was enhanced. In the sclerotic stage, the thickness of the skin layer was indeterminate, while the thickness of the subcutaneous fat layer was mildly reduced compared with that at peripheral control sites. The skin and subcutaneous tissue showed increased echogenicity due to greater collagen content in the dermis and hypodermis and sometimes superficial intramuscular hyperechogenicity. The blood flow signal of the skin was attenuated, and skin elasticity was moderately increased. Finally, ultrasonographic features of sclerodermatous skin in the atrophic phase demonstrated thinning of the dermis. The subcutaneous fat layer was shrunk or had disappeared, and apparent depressions may form in severe cases. Due to the disorganized accumulation of collagen, the echogenicity is significantly enhanced, with a prominent hyperelasticity. Finally, blood vessels and some cutaneous appendages may disappear with progression (**Fig. 1**; 19).

Psoriasis

Psoriasis is a chronic inflammatory disease that affects the skin of the scalp and appears over the extensor surface of the extremities as well as the nails, with pustular lesions or arthritic symptoms reported in a few cases

(25). The lesions are characterized by red patches of skin covered with thick, silvery hyperkeratotic scales. The bottom of the stripped scales is a light red translucent film (film phenomenon), and multiple punctate bleeding can be seen after scraping the film (Auspitz's sign) (26). Classic histopathology demonstrates hyperkeratosis and parakeratosis in the stratum corneum. There is often thickening of the epidermis, with elongated and clubbed rete ridges. The dermis often shows dilated capillaries and perivascular lymphocytes, and a relatively thin epidermis can be observed at the top of the dermal papillae (26). Ultrasound imaging characteristics (5, 27) are as follows: (i) epidermal thickening and enhanced echo are noted, corresponding to stratum corneum thickening in pathology; (ii) the dermis is thickened and hypoechoic due to the presence of inflammation and oedema; (iii) an anechoic band is visible at the dermal-epidermal junction, corresponding to inflammatory oedema and vasodilation, and has been reported as a reliable indicator of disease activity and a common ultrasonic feature (28, 29); (iv) elongated dilated and distorted capillary loops can be observed in the dermis with increased blood flow, especially during the active inflammatory phase of the disease (30). Furthermore, ultrasonographic imaging of psoriasis reveals pronounced inflammatory infiltrates, while the marked thickening of the epidermis with dilated and distorted vascular loops in the dermis are psoriasis-specific manifestations (**Fig. 2**; 27–30). For patients with psoriasis undergoing intervention, dermatologists are

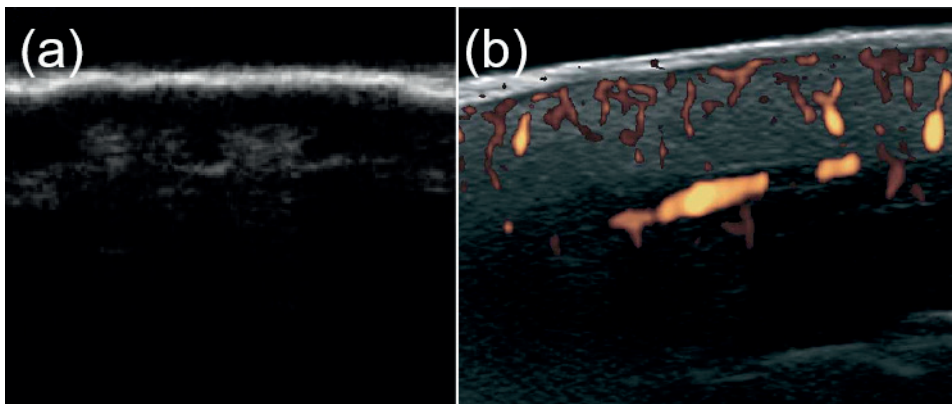


Fig. 2. (a) Psoriatic lesions: The epidermis is thickened and hyperechoic, the dermis is thickened and hypoechoic, and there is an anechoic band at the dermoepidermal junction (85). (b) In patients with psoriatic lesions, colour Doppler ultrasound reveals a highly vascular pattern within the dermis of psoriatic plaques (27). Red represents the blood flow of arteries.

advised to monitor local inflammatory activity regularly with HFUS for further evaluation of clinical efficacy. Approximately 90% of patients with psoriasis develop nail involvement during their lifetime (31). As a vital appendage of the skin, the ultrasound appearance of nails contributes to the diagnosis of psoriasis. Ventral nail plate deposits, irregular or fused nail plates, and increased nail plate thickness are frequently observed by ultrasound imaging of patients with psoriasis (32). Localized dimpling or loss of structure can be observed in patients with a longer duration of disease (33). Power Doppler imaging ultrasound detects the enhanced blood flow signal (32). Krajewska-Włodarczyk et al. (34) measured the thickness of the nail plate, nail bed, and matrix in psoriasis using HFUS, and these values were significantly greater than those of healthy controls. Sandobal et al. (35) defined a nail bed thickness >2.0 mm as the critical value to distinguish nail psoriasis, and confirmed that this standard has high diagnostic specificity and sensitivity. In addition, nail bed elasticity values were correlated with nail bed thickness and the Nail Psoriasis Severity Index score (NAPSI), which are used in the clinical evaluation of nail involvement (25). Nail psoriasis is often linked to a protracted duration of psoriasis and skin and joint involvement (36, 37). Therefore, while using HFUS to monitor the progress of skin lesions in patients, nail lesions should also be taken care of.

Dermatomyositis

Dermatomyositis is an autoimmune disease that causes skin changes and muscle weakness. The disease progresses from inflammation to fibrosis. Symptoms can include a reddish-purple rash around the eyelids, Gottron papules, and discoloured skin on the shoulders and neck (38, 39). Subcutaneous calcinosis can occasionally be seen, especially in juvenile dermatomyositis, and may result in pain, ulcerations, and infections (40). According to the histological description (41), patients with this condition have oedema present in the upper dermis and significant vacuolar interface change in the early stage, accompanied by extravasation of perivascular erythrocytes and inflammatory cells. However, later in the disease course, there is increased perivascular clustering, which leads to microinfarcts, necrosis, and hypoperfusion. Ischaemia and inflammatory infiltration can gradually cause the epidermis to atrophy and trigger fibrosis and atrophy of muscle fibres (42). In the acute phase, the epidermis of lesional skin appears thickened on ultrasound, echogenicity is increased, and blood flow is increased compared with healthy controls (43). There are also banded hypoechoic areas in the superficial dermis, which may be related to the expansion of epidermal capillaries and perivascular inflammation and oedema in the dermis (43). Finally, the subcutaneous diseased muscles are characterized by standard or slight swelling

size, hyperperfusion, and relatively low echogenicity (44). In the chronic phase, on ultrasound, the epidermis is atrophied and its thickness decreased, and the blood flow is diminished. The muscle shows decreased fullness and thickness, with decreased perfusion of surrounding blood. The muscularis presents diffuse increased echogenicity due to replacing atrophic or obliterated muscle fibres with large amounts of proliferative connective tissue (7, 45). In addition, persistent elastotic values are increased at the lesional site (46), corresponding to the disease's early inflammatory infiltration and late fibrotic course. In combination with calcinosis, intradermal hyperechoic masses with posterior acoustic shadowing are seen in lesional calcification (Fig. 3; 5, 47, 43, 48). Dermatomyositis sonographic manifestations vary with disease progression. Prompt diagnosis and intervention prior to lesion atrophy are beneficial to maintain limb function, prevent disability, and improve quality of life. Reimers et al. (7) reported that the sensitivity of sonography in detecting evidence of histopathologically proven dermatomyositis was not significantly different from that of electromyography or the measurement of creatine kinase activity. Furthermore, quantifying the distribution and degree of the lesion and variations in echo-intensity helps in assessing the disease's chronicity and severity and provides clues for assessing treatment effectiveness. Mittal et al. (49) recorded HFUS features at baseline and after 6 months of treatment in 11 patients with early, active, untreated inflammatory myopathies; all abnormalities of thigh muscles ultimately resolved with treatment.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune condition involving multiple organs and tissues throughout the body, with vasculitis recorded as the

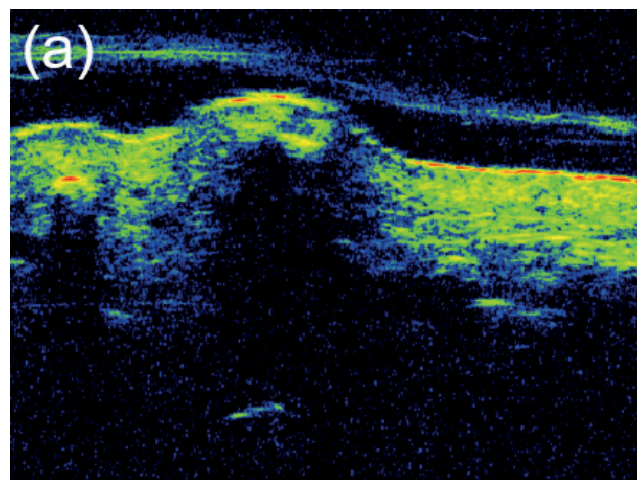


Fig. 3. In dermatomyositis lesions, epidermal thickening and echo enhancement are noted, and banded hypoechoic areas can be seen in the superficial dermis (43).

primary pathological manifestation. Typical symptoms include facial butterfly rash, palmar/plantar/periungual erythema, Raynaud's phenomenon, and nail fold microcirculation damage (50, 51). Some patients also present with deep subcutaneous nodules or plaques, also known as lupus panniculitis (50). Few reports have characterized the lupus facial erythema on ultrasound imaging, which may be consistent with most inflammatory dermatological manifestations, with variable thicknesses and echo intensities of all layers of the skin together with local blood flow signal enhancement (43). Lesion haemodynamic changes under ultrasound imaging in SLE are associated with vasculitis progression. Slight vessel spasms occur in the initial stage of the lesion; then, as the disease progresses, fibrinoid degeneration and vessel walls necrosis lead to thrombus formation and vessel occlusion (52). Zhang et al. (53) found that the vascular density at the fingertip of patients with SLE decreased, accompanied by distorted, thinner, and blurred blood flow signals. These authors (53) proposed that HFUS combined with colour Doppler can quantitatively detect early lesions of microvessels. Li et al. (54) found that, compared with the control group, the peak systolic velocity and the end-diastolic velocity of finger lesions in SLE were decreased, while the resistance index was increased, indicating that the blood vessel wall was damaged obviously and its elasticity was poor. The counterpart clinical manifestations include periungual erythema, purpuric rash, and even cutaneous ulceration or acral gangrene. In addition, under ultrasound imaging, oedema and thickening in the fingers' soft tissues, accompanied by echo attenuation and knuckle lesions, may be observed (54). Kimball et al. (55) reported a patient with facial lupus panniculitis whose ultrasound demonstrated a slightly hyperechoic ovoid pseudo-mass-like lesion, wrapped by the surrounding subcutaneous fat with a thin hypoechoic edge. There was increased vascularity at the centre of the lesion on Doppler evaluation without any displacement of vascular structures (**Fig. 4**;

55). Due to the lack of specificity, the value of HFUS in SLE lesion diagnosis requires further exploration. However, HFUS can quantitatively assess the strength and distribution of blood flow signals, showing potential in monitoring the progression of vasculitis in SLE skin lesions.

Pemphigus/pemphigoid

Bullous dermatoses refer to a group of skin disorders that occur on the skin or mucosa, with blisters and bullae appearing as the underlying skin lesions. Both pemphigus and pemphigoid are categorized as autoimmune bullous skin diseases. Pemphigus mainly appears as thin-walled, flaccid blisters and bullae on skin or mucosa with a positive Nissl sign. These blisters rupture easily due to erosion, do not heal quickly, and can be co-infected (56). Pathologically, pemphigus is characterized by intraepithelial clefts or blisters and acantholysis (57). Prior to the appearance of typical bullae and mucosal lesions, pemphigus is often characterized by erythema and erosion on the skin during their early stage. Zheng et al. (58) reported ultrasonographic characteristics of early erythema in patients with pemphigus vulgaris (PV), including slightly increased dermal thickness, and a reduced echo of the superficial dermis relative to the whole dermis. Meanwhile, a linear hypoechoic area was found at the junction between the dermis and epidermis, suggesting the presence of inflammation and oedema in the upper dermis (43). In research, linear intra-epidermal anechoic bands and banded hypoechoic areas beneath the epidermis showed the greatest specificity in the differentiation from other erythematous disorders, consistent with the histopathological features of intra-epidermal fissures (58). As blisters form, skin ultrasound showed semi-arcuate anechoic areas with clear borders in the epidermis and a distinct hyperechoic line at the base of the anechoic area, suggesting that the blisters were located within the epidermis. Pemphigoid

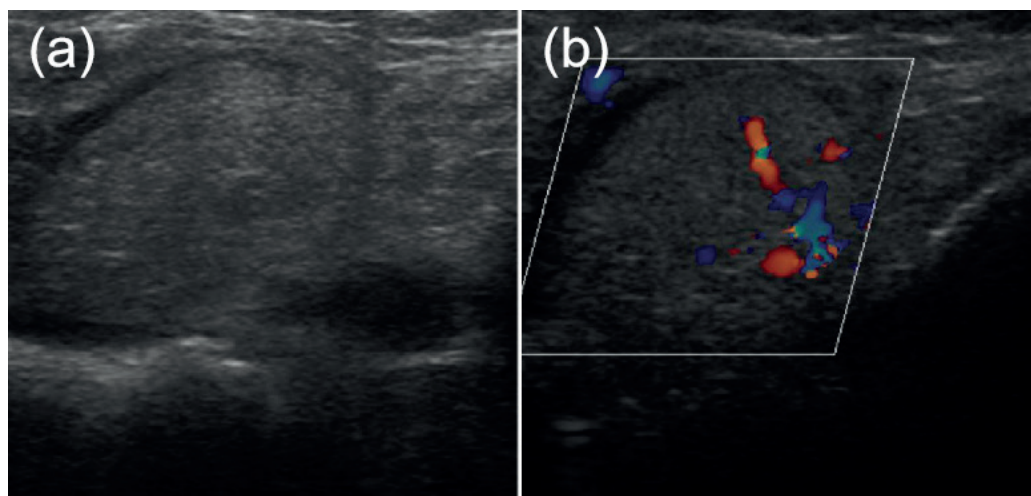


Fig. 4. (a) In lupus panniculitis, a slightly hyperechoic ovoid pseudo-mass-like lesion, wrapped by the surrounding subcutaneous fat with a thin hypoechoic edge, is seen. (b) In lupus panniculitis, colour Doppler ultrasound demonstrates enhanced blood flow signals (55). Red represents arteries and blue represents veins.

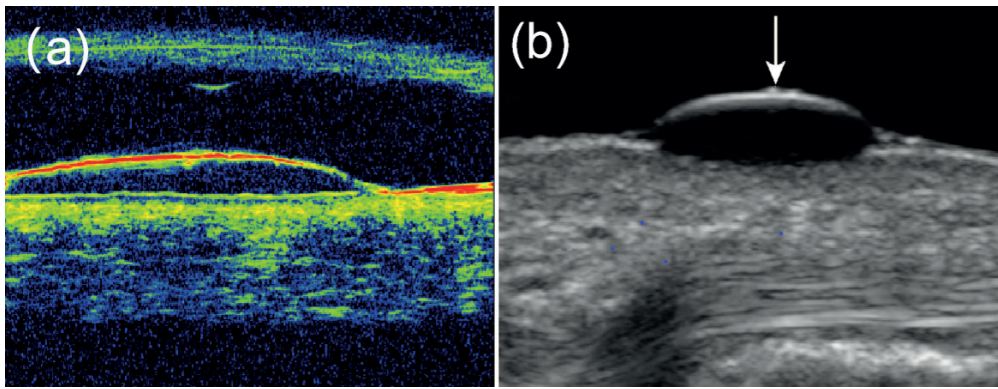


Fig. 5. (a) In patients with pemphigus lesions, semi-arcuate anechoic areas with clear borders in the epidermis and a distinct hyperechoic line at the base of the anechoic area can be seen (43). (b) In patients with pemphigoid lesions, a continuous intact epidermis and oval hypoechoic areas beneath the epidermis (white arrow) with clear borders are present (59).

mainly involve the skin, with relatively little involvement of mucous membranes. These tight, thick-walled blisters or bullae based on normal skin or erythema do not break easily, and their erosive surface heals easily, resulting in less frequent infection (56). The vesicular Nissl sign experiment is negative. Histopathologically, inflammatory cells, including eosinophils, infiltrate into the subepidermal blisters and upper dermis. A few reports on the sonographic features associated with the erythematous phase of pemphigoid are available. Skin ultrasound suggested a continuous intact epidermis with increased blood flow in the superficial dermis. With the appearance of blisters, there are oval hypoechoic areas present beneath the epidermis, with clear borders (**Fig. 5**; 7, 43, 59). Cheng et al. (60) used HFUS to distinguish the location of blisters in patients with bullous dermatosis, and good concordance between HFUS and histology was noted. Izzetti et al. (61) performed ultrasonographic examinations of oral endothelial lesions in 25 patients with pemphigus or pemphigoid and found that ultra-HFUS shows 75% and 66.7% sensitivity in the diagnosis, respectively. Ultra-HFUS also appears effective for detecting whether bullae are intraepithelial or subepithelial; the lesions' echogenicity and the differences in grey level distribution can help in differential

diagnosis. Also, the size and shape of these hypoechoic/anechoic areas located in or beneath the epidermis are closely correlated with the disease stage (58).

DISCUSSION

As a non-invasive and reproducible imaging technology, the application of HFUS avoids unsightly cosmetic consequences or unrepeatable sampling of affected tissues, significantly improves the acceptability of operation, reduces the difficulty of early diagnosis, and allows for more timely intervention and optimal patient prognosis management. Several other non-invasive imaging modalities have been employed to assess skin lesions, such as confocal laser microscopy and optical coherence tomography. Both reflectance confocal microscopy and optical coherence tomography provide enhanced tissue resolution, but limited penetration to identify deep dermal and subcutaneous lesions (62). Among them, a wide range of frequency options allows the HFUS to balance the imaging resolution and the penetration depth of tissues better (**Table I**). HFUS provides dermatologists with multi-dimensional and sensitive visual information, including thickness, boundary, elasticity, echogenicity, and blood flow. Dermatologists summarize this infor-

Table I. Typical high-frequency ultrasound manifestations of autoimmune dermatoses

	Skin lesions ultrasound manifestations	Ultrasound frequency recommendation
Scleroderma (oedematous phase)	Thickened dermis, hypoechoic, slightly increased elasticity, and enhanced blood flow signal	Use 20–22 MHz ultrasound due to significant alterations in the dermis
Scleroderma (sclerotic phase)	Hyperechoic dermis, moderately increased elasticity, and attenuated blood flow signal	Use 15–18 MHz ultrasound when lesions involve deeper subcutaneous soft tissues, whereas 20–22 MHz ultrasound is reasonable when lesions are limited to the skin
Scleroderma (atrophic phase)	Atrophic skin, hyperechoic dermis, markedly increased elasticity, and weak or absent blood flow signal	Use 15–18 MHz ultrasound when lesions involve deeper subcutaneous soft tissues, whereas 20–22 MHz ultrasound is reasonable when lesions are limited to the skin
Psoriasis	Markedly thickened epidermis with hyperechoic characteristic; thickened dermis with hypoechoic, anechoic band at the dermoepidermal junction; and dilated and twisted capillaries	Use 22–25 MHz ultrasound when keratosis and hypertrophy are obvious
Dermatomyositis	Thickened and hyperechoic epidermis, hypoechoic band in the upper dermis; intradermal hyperechoic mass with posterior acoustic shadowing in lesional calcification	Use 12–20 MHz ultrasound because of the occurrence of simultaneous cutaneous and subcutaneous muscle lesions
Systemic lupus erythematosus	Limited research; decreased vascular density, weakened and blurred blood flow signals at the fingertip lesions	Use 15–22 MHz ultrasound according to the extent of lesional infiltration
Pemphigus	Semi-arcuate anechoic areas with clear borders in the epidermis, distinct hyperechoic line at the base of the anechoic area	Use 50–75 MHz ultrasound for observation because it is necessary to accurately judge the location of superficial blisters
Pemphigoid	Continuous intact epidermis and oval, hypoechoic areas beneath the epidermis with clear borders; increased blood flow in the superficial dermis	Use 50–75 MHz ultrasound for observation because it is necessary to accurately judge the location of superficial blisters

Table II. Summary of benefits and limitations of common non-invasive imaging techniques used in dermatology

Non-invasive imaging techniques	Maximum penetration depth, mm	Maximum resolution, μm	Benefits	Limitations
Reflectance confocal microscopy (63–69)	0.2	0.5–1	High sensitivity and specificity. Close to histologic resolution. Can help distinguish between benign and malignant lesions.	Limited depth of visualization. Expensive equipment and a need of expertise. Difficultly in use in the presence of ulceration, hyperkeratosis, or dense pigmentation.
High-definition optical coherence tomography (70, 71)	0.57	<3	Improve earlier detection of skin cancer. Can decrease biopsy rate.	Lower resolution than RCM. Cannot produce quality images of lesions with crust or hyperkeratosis.
Optical coherence tomography (63, 72–76)	2	4–10	Can evaluate the scope of lesion surgery. Can be used to monitor the effectiveness of nonsurgical treatments.	
High-frequency ultrasound (3, 77–81)	50	40	High sensitivity, with average specificity. Good resolution for the visualization of superficial skin structures. Can observe different levels of lesions, and can be used with a wide range of ultrasound frequency options according to needs. Can help diagnose and monitor common inflammatory and autoimmune dermatoses. The elastography is a unique technique of skin fibrosis assessment through the evaluation of skin strain.	Operator-dependent. Lower resolution than RCM and OCT. Lack of specific diagnostic indicators.
Computed tomography (63, 82)	Total body penetration	100	Augment the visualization of deeper structures	Expensive modalities and lack adequate resolution providing useful information.
Magnetic resonance imaging (63, 82)	Total body penetration	100		

RCM: reflectance confocal microscopy; OCT: optical coherence tomography.

mation to stage the skin lesion of scleroderma, from the oedematous phase to the sclerotic and the atrophic stage. HFUS as well acts as a significant role in evaluating the inflammatory activity and severity of lesions in diseases, such as dermatomyositis, psoriasis, and SLE. HFUS has also been used to distinguish the location of blisters in patients with bullous dermatosis, which promotes the differential diagnosis of bullous disease. In the meantime, HFUS facilitates the development of teler dermatology as it can be used in an asynchronous store and forward manner, giving patients the possibility of being examined, monitored, and managed by a medical expert in a distant location (3).

HFUS has some limitations (Table II; 63–82). HFUS is of particular value in the diagnosis and differential diagnosis of skin cancer, especially melanoma. Compared with melanoma, benign tumours tend to have more internal echoes. Numerous hyperechoic spots are considered to be a characteristic feature enabling HFUS differentiation of basal cell carcinoma from melanoma. HFUS can differentiate benign and malignant skin lesions through recognition of specific ultrasonic features and define lesions boundary for surgery (27, 83, 84). In contrast to skin cancer, HFUS has a lack of specific diagnostic indicators in autoimmune diseases. Further studies, including more extensive case series, need to be conducted to better define HFUS features of autoimmune dermatoses. Currently, the specialization in dermatology and sonography limits the universal use of skin ultrasonography. Therefore, timely professional communication between the 2 disciplines is recommended to establish a complete ultrasound assessment system for dermatology and to help create guidelines for implementing this technique in clinical practice.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (numbers 82003363, 81773333, 82073449, and 82001738), the Hunan Provincial Natural Science Foundation of China (2021JJ40820), and the Changsha Municipal Natural Science Foundation (kq2007059).

The authors have no conflicts of interest to declare.

REFERENCES

- Vesely MD. Getting under the skin: targeting cutaneous autoimmune disease. *Yale J Biol Med* 2020; 93: 197–206.
- Chiorean R, Mahler M, Sitaru C. Molecular diagnosis of autoimmune skin diseases. *Rom J Morphol Embryol* 2014; 55: 1019–1033.
- Polańska A, Jenerowicz D, Paszyńska E, Żaba R, Adamski Z, Dańczak-Pazdrowska A. High-frequency ultrasonography-possibilities and perspectives of the use of 20 MHz in teler dermatology. *Front Med (Lausanne)* 2021; 8: 619965.
- Almuhanna N, Wortsman X, Wohlmuth-Wieser I, Kinoshita-Ise M, Alhusayen R. Overview of ultrasound imaging applications in dermatology [Formula: see text]. *J Cutan Med Surg* 2021; 25: 521–529.
- Alfageme F, Wortsman X, Catalano O, Roustan G, Crisan M, Crisan D, et al. European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) position statement on dermatologic ultrasound. *Ultraschall Med* 2021; 42: 39–47.
- Kleinerman R, Whang TB, Bard RL, Marmur ES. Ultrasound in dermatology: Principles and applications. *Journal of the American Academy of Dermatology* 2012; 67: 478–487.
- Reimers CD, Fleckenstein JL, Witt TN, Muller-Felber W, Pongratz DE. Muscular ultrasound in idiopathic inflammatory myopathies of adults. *J Neurol Sci* 1993; 116: 82–92.
- Barcaui EO, Carvalho AC, Lopes FP, Pineiro-Maceira J, Barcaui CB. High frequency ultrasound with color Doppler in dermatology. *An Bras Dermatol* 2016; 91: 262–273.
- Wortsman X, Wortsman J. Clinical usefulness of variable-frequency ultrasound in localized lesions of the skin. *J Am Acad Dermatol* 2010; 62: 247–256.
- Rallan D, Harland CC. Ultrasound in dermatology – basic

- principles and applications. *Clin Exp Dermatol* 2003; 28: 632–638.
11. Schneider SL, Kohli I, Hamzavi IH, Council ML, Rossi AM, Ozog DM. Emerging imaging technologies in dermatology: Part I: Basic principles. *J Am Acad Dermatol* 2019; 80: 1114–1120.
 12. Burns PN. Principles of Doppler and color flow. *Radiol Med* 1993; 85: 3–16.
 13. Gennisson JL, Deffieux T, Fink M, Tanter M. Ultrasound elastography: principles and techniques. *Diagn Interv Imaging* 2013; 94: 487–495.
 14. Zhang X, Zhou B, Osborn T. Ultrasound surface wave elastography for assessing scleroderma. *Ultrasound Med Biol* 2020; 46: 1263–1269.
 15. Sigrist R, Liao J, Kaffas AE, Chammas MC, Willmann JK. Ultrasound elastography: review of techniques and clinical applications. *Theranostics* 2017; 7: 1303–1329.
 16. Taljanovic MS, Gimber LH, Becker GW, Latt LD, Klauser AS, Melville DM, et al. Shear-wave elastography: basic physics and musculoskeletal applications. *Radiographics* 2017; 37: 855–870.
 17. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72: 1747–1755.
 18. Rongioletti F, Ferrelli C, Atzori L, Bottoni U, Soda G. Scleroderma with an update about clinico-pathological correlation. *G Ital Dermatol Venereol* 2018; 153: 208–215.
 19. Chiu YE, Abban CY, Konicke K, Segura A, Sokumbi O. Histopathologic spectrum of morphea. *Am J Dermatopathol* 2021; 43: 1–8.
 20. Li H, Furst DE, Jin H, Sun C, Wang X, Yang L, et al. High-frequency ultrasound of the skin in systemic sclerosis: an exploratory study to examine correlation with disease activity and to define the minimally detectable difference. *Arthritis Res Ther* 2018; 20: 181.
 21. Wortsman X, Wortsman J, Sazunic I, Carreno L. Activity assessment in morphea using color Doppler ultrasound. *J Am Acad Dermatol* 2011; 65: 942–948.
 22. Zhang X, Zhou B, Osborn T, Bartholmai B, Kalra S. Lung ultrasound surface wave elastography for assessing interstitial lung disease. *IEEE Trans Biomed Eng* 2019; 66: 1346–1352.
 23. Ruaro B, Santiago T, Hughes M, Lepri G, Poillucci G, Baratella E, et al. The updated role of ultrasound in assessing dermatological manifestations in systemic sclerosis. *Open Access Rheumatol* 2021; 13: 79–91.
 24. Li SC, Liebling MS. The use of Doppler ultrasound to evaluate lesions of localized scleroderma. *Curr Rheumatol Rep* 2009; 11: 205–211.
 25. Asil K, Yaldiz M. Diagnostic role of ultrasound elastography for nail bed involvement in psoriasis. *Medicine (Baltimore)* 2019; 98: e17917.
 26. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis* 2005; 64: ii18–23; discussion ii24–15.
 27. Wortsman X. Common applications of dermatologic sonography. *J Ultrasound Med* 2012; 31: 97–111.
 28. Di Nardo A, Seidenari S, Giannetti A. B-scanning evaluation with image analysis of psoriatic skin. *Exp Dermatol* 1992; 1: 121–125.
 29. Vaillant L, Berson M, Machel L, Callens A, Pourcelot L, Lorette G. Ultrasound imaging of psoriatic skin: a noninvasive technique to evaluate treatment of psoriasis. *Int J Dermatol* 1994; 33: 786–790.
 30. Gupta AK, Turnbull DH, Harasiewicz KA, Shum DT, Watteel GN, Foster FS, et al. The use of high-frequency ultrasound as a method of assessing the severity of a plaque of psoriasis. *Arch Dermatol* 1996; 132: 658–662.
 31. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 2008; 58: 826–850.
 32. Marina ME, Solomon C, Bolboaca SD, Bocsa C, Mihu CM, Tataru AD. High-frequency sonography in the evaluation of nail psoriasis. *Med Ultrason* 2016; 18: 312–317.
 33. Aydin SZ, Castillo-Gallego C, Ash ZR, Abignano G, Marzo-Ortega H, Wittmann M, et al. Potential use of optical coherence tomography and high-frequency ultrasound for the assessment of nail disease in psoriasis and psoriatic arthritis. *Dermatology* 2013; 227: 45–51.
 34. Krajewska-Wlodarczyk M, Owczarczyk-Saczonek A, Placek W, Wojtkiewicz M, Wiktorowicz A, Wojtkiewicz J. Ultrasound assessment of changes in nails in psoriasis and psoriatic arthritis. *Biomed Res Int* 2018; 2018: 8251097.
 35. Sandobal C, Carbo E, Iribas J, Roverano S, Pairs S. Ultrasound nail imaging on patients with psoriasis and psoriatic arthritis compared with rheumatoid arthritis and control subjects. *J Clin Rheumatol* 2014; 20: 21–24.
 36. Armesto S, Esteve A, Coto-Segura P, Drake M, Galache C, Martinez-Borra J, et al. [Nail psoriasis in individuals with psoriasis vulgaris: a study of 661 patients]. *Actas Dermosifiliogr* 2011; 102: 365–372 (in Spanish).
 37. McGonagle D, Ash Z, Dickie L, McDermott M, Aydin SZ. The early phase of psoriatic arthritis. *Ann Rheum Dis* 2011; 70: i71–76.
 38. DeWane ME, Waldman R, Lu J. Dermatomyositis: Clinical features and pathogenesis. *J Am Acad Dermatol* 2020; 82: 267–281.
 39. Muro Y, Sugiura K, Akiyama M. Cutaneous manifestations in dermatomyositis: key clinical and serological features – a comprehensive review. *Clin Rev Allergy Immunol* 2016; 51: 293–302.
 40. Chung MP, Richardson C, Kirakossian D, Orandi AB, Sackett LA, Rider LG, et al. Calcinosis biomarkers in adult and juvenile dermatomyositis. *Autoimmun Rev* 2020; 19: 102533.
 41. Hou Y, Luo YB, Dai T, Shao K, Li W, Zhao Y, et al. Revisiting pathological classification criteria for adult idiopathic inflammatory myopathies: in-depth analysis of muscle biopsies and correlation between pathological diagnosis and clinical manifestations. *J Neuropathol Exp Neurol* 2018; 77: 395–404.
 42. Dalakas MC, Hohlfield R. Polymyositis and dermatomyositis. *Lancet* 2003; 362: 971–982.
 43. Ran M, Li H, Lu M. Expert consensus on high-frequency ultrasound diagnosis of common skin diseases. *Chin J Frontiers Med Sci* 2019; 11: 23–28.
 44. Kolasinski SL, Chi AS, Lopez-Garib AJ. Current perspectives on imaging for systemic lupus erythematosus, systemic sclerosis, and dermatomyositis/polymyositis. *Rheum Dis Clin North Am* 2016; 42: 711–732.
 45. Sudol-Szopinska I, Jacques T, Gietka P, Cotten A. Imaging in dermatomyositis in adults and children. *J Ultrason* 2020; 20: e36–e42.
 46. Song Y, Lee S, Yoo DH, Jang KS, Bae J. Strain sonoelastography of inflammatory myopathies: comparison with clinical examination, magnetic resonance imaging and pathological findings. *Br J Radiol* 2016; 89: 20160283.
 47. Suliman YA, Kafaja S, Fitzgerald J, Wortsman X, Grotts J, Matucci-Cerrinic M, et al. Ultrasound characterization of cutaneous ulcers in systemic sclerosis. *Clin Rheumatol* 2018; 37: 1555–1561.
 48. Lorente-Luna M, Alfageme RF, Gonzalez LC. Ultrasound diagnosis of calcified skin deposits. *Actas Dermosifiliogr* 2015; 106: 586–588.
 49. Mittal GA, Wadhvani R, Shroff M, Sukthankar R, Pathan E, Joshi VR. Ultrasonography in the diagnosis and follow-up of idiopathic inflammatory myopathies – a preliminary study. *J Assoc Physicians India* 2003; 51: 252–256.
 50. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am* 2012; 59: 345–364.
 51. van Vollenhoven R, Voskuyl A, Bertsias G, Aranow C, Aringer M, Arnaud L, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis* 2017; 76: 554–561.
 52. Guillevin L, Dorner T. Vasculitis: mechanisms involved and clinical manifestations. *Arthritis Res Ther* 2007; Suppl 2: S9.

53. Zhang Y, Lv Q, Xie M, Wang X, Xiang F, Lu C, et al. Investigation of fingertip vascular changes in patients with systemic lupus erythematosus by high-frequency ultrasonography in combination with quantitative studies of blood flow. *Radiol Practice* 2009; 24: 331–333.
54. Li Q. The value of color Doppler ultrasound in monitoring the renal impairment in systemic lupus erythematosus by testing. *Chinese Imag J Integr Tradit Western Med* 2017; 15: 302–304.
55. Kimball H, Kimball D, Siroy A, Tuna IS, Boyce BJ, Albayram MS. Novel diagnostic imaging features of facial lupus panniculitis: ultrasound, CT, and MR imaging with histopathology correlate. *Clin Imaging* 2019; 58: 177–181.
56. Kneisel A, Hertl M. Autoimmune bullous skin diseases. Part 1: clinical manifestations. *J Dtsch Dermatol Ges* 2011; 9: 844–856; quiz 857.
57. Kneisel A, Hertl M. Autoimmune bullous skin diseases. Part 2: diagnosis and therapy. *J Dtsch Dermatol Ges* 2011; 9: 927–947.
58. Zheng X, Wu C, Jin H, Liu J, Wang H. Investigation of using very high-frequency ultrasound in the differential diagnosis of early-stage pemphigus vulgaris vs seborrheic dermatitis. *Skin Res Technol* 2020; 26: 476–481.
59. Guo R, Qiu L. Ultrasonic manifestations of bullous pemphigoid: case report. *Chin J Med Imag Technol* 2018; 34: 1743.
60. Cheng X, Li J, Zhou G, Liu Y, Lu X, Wang N, et al. High-frequency ultrasound in blistering skin diseases: a useful method for differentiating blister locations. *J Ultrasound Med* 2017; 36: 2367–2371.
61. Izzetti R, Nisi M, Aringhieri G, Vitali S, Oranges T, Romanelli M, et al. Ultra-high frequency ultrasound in the differential diagnosis of oral pemphigus and pemphigoid: An explorative study. *Skin Res Technol* 2021; 27: 682–691.
62. Heibel HD, Hooley L, Cockerell CJ. A review of noninvasive techniques for skin cancer detection in dermatology. *Am J Clin Dermatol* 2020; 21: 513–524.
63. Dalimier E, Salomon D. Full-field optical coherence tomography: a new technology for 3D high-resolution skin imaging. *Dermatology* 2012; 224: 84–92.
64. Sahu A, Yélamos O, Iftimia N, Cordova M, Alessi-Fox C, Gill M, et al. Evaluation of a combined reflectance confocal microscopy-optical coherence tomography device for detection and depth assessment of basal cell carcinoma. *JAMA Dermatol* 2018; 154: 1175–1183.
65. Haroon A, Shafi S, Rao BK. Using reflectance confocal microscopy in skin cancer diagnosis. *Dermatol Clin* 2017; 35: 457–464.
66. Borsari S, Pampena R, Lallas A, Kyrgidis A, Moscarella E, Benati E, et al. Clinical indications for use of reflectance confocal microscopy for skin cancer diagnosis. *JAMA Dermatol* 2016; 152: 1093–1098.
67. Guiler JM, Barreiro Capurro A, Carrera Álvarez C, Puig Sardá S. The role of reflectance confocal microscopy in clinical trials for tumor monitoring. *Dermatol Clin* 2016; 34: 519–526.
68. Star P, Guitera P. Lentigo maligna, macules of the face, and lesions on sun-damaged skin: confocal makes the difference. *Dermatol Clin* 2016; 34: 421–429.
69. Gill M, González S. Enlightening the pink: use of confocal microscopy in pink lesions. *Dermatol Clin* 2016; 34: 443–458.
70. Boone M, Norrenberg S, Jemec G, Del Marmol V. High-definition optical coherence tomography: adapted algorithmic method for pattern analysis of inflammatory skin diseases: a pilot study. *Arch Dermatol Res* 2013; 305: 283–297.
71. Boone MALM, Norrenberg S, Jemec GBE, Del Marmol V. High-definition optical coherence tomography imaging of melanocytic lesions: a pilot study. *Arch Dermatol Res* 2014; 306: 11–26.
72. Ulrich M, von Braunmuehl T, Kurzen H, Dirschka T, Kellner C, Sattler E, et al. The sensitivity and specificity of optical coherence tomography for the assisted diagnosis of nonpigmented basal cell carcinoma: an observational study. *Br J Dermatol* 2015; 173: 428–435.
73. Tankam P, Soh J, Canavesi C, Lanis M, Hayes A, Cogliati A, et al. Gabor-domain optical coherence tomography to aid in Mohs resection of basal cell carcinoma. *Journal of the Amer Acad Dermatol* 2019; 80: 1766–1769.
74. Boone MALM, Suppa M, Pellacani G, Marneffe A, Miyamoto M, Alarcon I, et al. High-definition optical coherence tomography algorithm for discrimination of basal cell carcinoma from clinical BCC imitators and differentiation between common subtypes. *J Eur Acad Dermatol Venereol* 2015; 29: 1771–1780.
75. Cheng HM, Lo S, Scolyer R, Meekings A, Carlos G, Guitera P. Accuracy of optical coherence tomography for the diagnosis of superficial basal cell carcinoma: a prospective, consecutive, cohort study of 168 cases. *Br J Dermatol* 2016; 175: 1290–1300.
76. Maher NG, Blumetti TP, Gomes EE, Cheng HM, Satgunaseelan L, Lo S, et al. Melanoma diagnosis may be a pitfall for optical coherence tomography assessment of equivocal amelanotic or hypomelanotic skin lesions. *Br J Dermatol* 2017; 177: 574–577.
77. Crisan M, Crisan D, Sannino G, Lupsor M, Badea R, Amzica F. Ultrasonographic staging of cutaneous malignant tumors: an ultrasonographic depth index. *Arch Dermatol Res* 2013; 305: 305–313.
78. Kozárová A, Kozár M, Tonhajzerová I, Pappová T, Minariková E. The value of high-frequency 20 MHz ultrasonography for preoperative measurement of cutaneous melanoma thickness. *Acta Dermatovenerol Croat* 2018; 26: 15–20.
79. Meyer N, Lauwers-Cances V, Lourari S, Laurent J, Konstantinou MP, Lagarde JM, et al. High-frequency ultrasonography but not 930-nm optical coherence tomography reliably evaluates melanoma thickness in vivo: a prospective validation study. *Br J Dermatol* 2014; 171: 799–805.
80. Sobolewski P, Maślińska M, Zakrzewski J, Paluch Ł, Szymańska E, Walecka I. Applicability of shear wave elastography for the evaluation of skin strain in systemic sclerosis. *Rheumatol Int* 2020; 40: 737–745.
81. Sobolewski P, Elżbieta Dźwigala M, Maślińska M, Szymańska E, Walecka I. How to perform high ultrasound examination of skin involvement among patients with systemic sclerosis – proposition of a unified protocol. *Reumatologia* 2021; 59: 9–11.
82. Longo C, Lallas A, Kyrgidis A, Rabinovitz H, Moscarella E, Ciardo S, et al. Classifying distinct basal cell carcinoma subtype by means of dermatoscopy and reflectance confocal microscopy. *J Amer Acad Dermatol* 2014; 71: 716–724.
83. Piłat P, Borzęcki A, Jazienicki M, Gerkowicz A, Krasowska D. High-frequency ultrasound in the diagnosis of selected non-melanoma skin nodular lesions. *Postepy Dermatol Alergol* 2019; 36: 572–580.
84. Pathania YS, Apalla Z, Salerni G, Patil A, Grabbe S, Goldust M. Non-invasive diagnostic techniques in pigmentary skin disorders and skin cancer. *J Cosmet Dermatol* 2022; 21: 444–450.
85. Niu Z, Wang Y, Zhu Q, Liu J, Liu Y, Jin H. The value of high-frequency ultrasonography in the differential diagnosis of early mycosis fungoides and inflammatory skin diseases: a case-control study. *Skin Res Technol* 2021; 27: 453–460.