Role of Ultrasound at 50 MHz in Skin Cancer

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Skin cancer, or cutaneous carcinoma, represents the most common malignancy that affects every race worldwide, mainly divided into two groups, namely non-melanoma skin cancer (NMSC) and malignant melanoma (MM) [1, 2]. Among them, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the first and the second most frequently encountered entities in clinical practice, respectively [3]. MM is relatively rare, but MM still gained much attention because it is the most lethal skin cancer, and the incidence of MM is constantly increasing [4].

As discussed earlier, high-frequency ultrasound (HFUS) has been successfully employed to accurately detect and diagnose BCC, SCC, and MM lesions. Generally, broadband, linear transducers with frequencies at around 15–30 MHz are most commonly used for skin disorder assessment. With higher frequency, the spatial resolution gets promoted at the cost of penetration (3 mm at 75 MHz and 1 mm at 100 MHz). Nevertheless, variable-frequency probes may decrease this loss of penetration. Of note, it is of vital importance to explore the deep dermis and subcutaneous tissue, especially when assessing skin cancers, since they tend to involve deeper structures aggressively. Besides, small lesions might not be connected to the corresponding main lesions and would be missed by ultrasound if excessively high-frequency probes were used. However, for superficial skin cancers where a deeper extension has been ruled out, higher frequencies can provide clinicians with more detailed information about the morphological features of small lesions as well as the subtle alterations of superficial skin structures that can be helpful for the accurate assessment, differential diagnosis, and histopathological subtype speculation. Therefore, it is suggested that the operator starts the ultrasonic investigations with the lower frequency range to fully assess the involved areas, exclude deeper invasion, and then switch to a higher frequency to appreciate the details of lesions and areas of interest [5].

Additionally, recent studies have investigated HFUS application of primary cutaneous lymphoma (PCL), a special entity of skin malignancies, especially mycosis fungoides (MF). This chapter mainly discusses the application values and merits of 50 MHz HFUS in BCC, SCC, MM, and MF.

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Basal Cell Carcinoma

Under HFUS scanning, BCC lesions typically manifest as oval or band-like hypoechoic structures accompanied by hyperechoic spots with

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slightly irregular borders within the dermis or extending into the subcutaneous tissue [6, 7] (Figs. 14.1 and 14.2). Histologically, these hyperechoic spots are speculated to be related to several intrinsic features of BCC lesions, including keratosis, melanin, microcalcification, and clusters of apoptotic cells in the centers of nests of basaloid cells, but the exact mechanisms are yet to be established [8, 9].

Several studies have applied 50 MHz HFUS in assessing BCC lesions [10–12], where the sonographic morphological details and features in the different histopathological subtypes are revealed better with a higher resolution [11]. Nodular BCCs appeared as irregular, oval, or band-like hypoechoic areas, mostly well defined with heterogeneous internal echogenicity (sometimes harboring internal anechoic zones) and several hyperechoic spots. Superficial BCCs are revealed as well-defined homogeneous hypoechoic band-like zones without internal echoes. Micro-nodular BCCs manifest as ill-defined small hypoechoic dermal structures accompanied by hyperechoic spots and posterior enhancement artifacts. Infiltrative BCCs are characterized as ill-defined, irregular hypodermal areas with many hyperechoic spots. Basosquamous cell carcinoma appeared as ill-defined dermal and hypodermal nodules with multiple hyperechoic spots and anechoic areas inside the lesion. As for the classification of low or high risk of recurrence, lesions from the former group tend to be regular in shape,

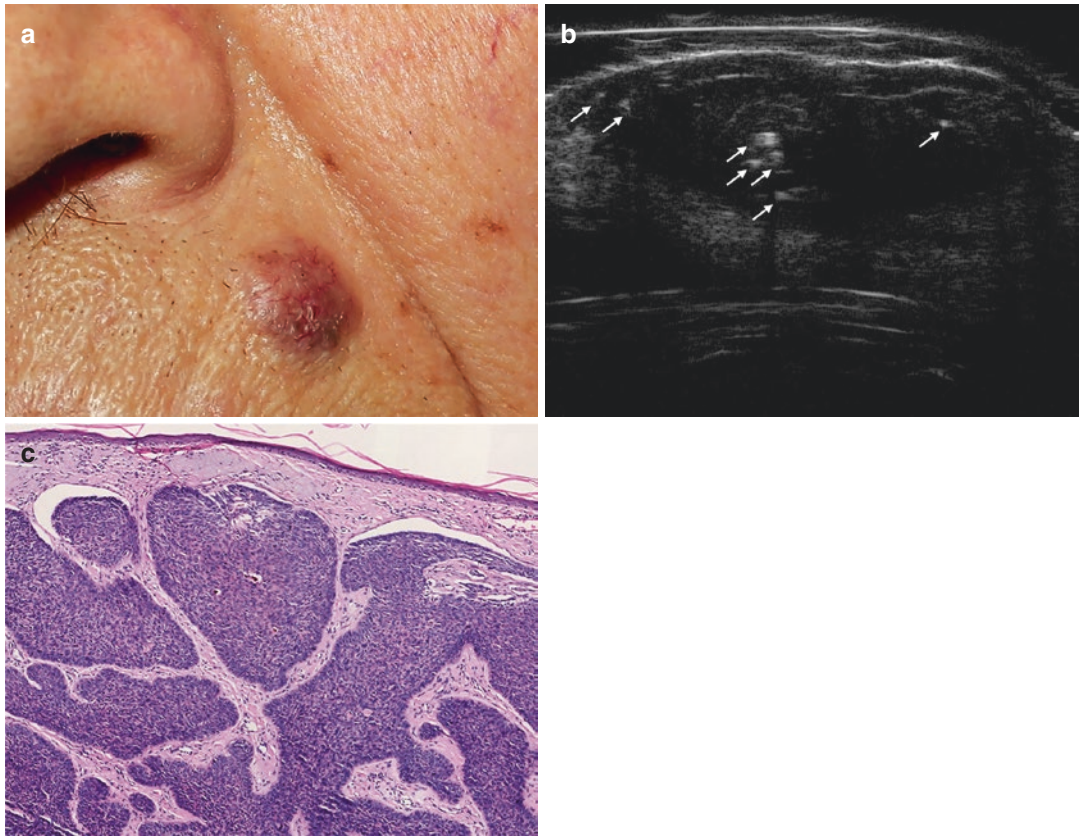

Fig. 14.1 Basal cell carcinoma of low-risk-of-recurrence type (nodular type in histopathology). (**a**) The clinical image shows an elevated erythematous nodule on the nasolabial fold, with fine scales, pigmentation, and telangiectasis. (**b**) High-frequency ultrasound at 50 MHz reveals a well-defined, slightly irregular hypoechoic structure in the dermis with multiple hyperechoic spots (arrows). (**c**) The histopathologic investigation confirmed the diagnosis of nodular basal cell carcinoma, showing multiple large nests of basaloid cells in the dermis (HE, ×25)

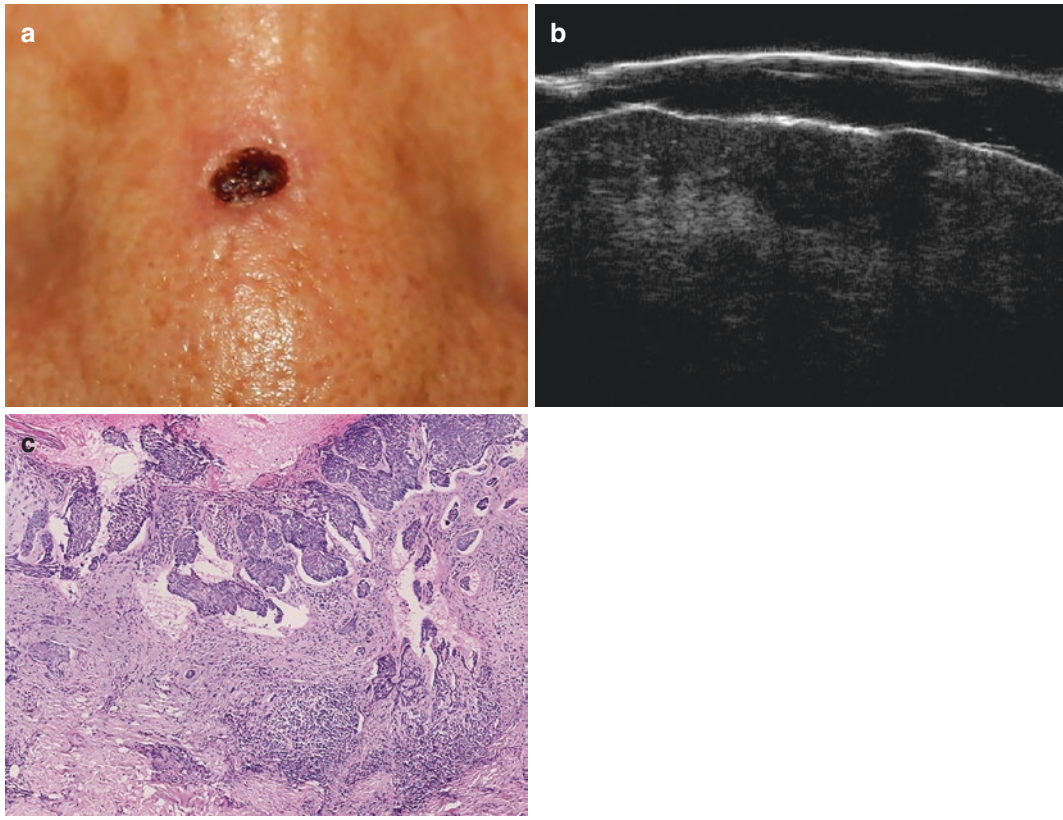

Fig. 14.2 Basal cell carcinoma of high-risk-of-recurrence type (infiltrative type in histopathology). (**a**) The clinical image shows ulceration with a sharp margin on the nasal dorsum. (**b**) High-frequency ultrasound at 50 MHz reveals an ill-defined, irregular-shaped, hypoechoic structure extending into the subcutaneous tissue, with a large number of hyperechoic spots. (**c**) Histopathology indicated the diagnosis of infiltrative basal cell carcinoma, where tumor cells are sometimes arranged in an irregular and strand pattern with a tendency to involve a deeper layer (HE, ×25)

with clear boundaries and homogeneous internal echogenicity, confined to the subepidermal area and the dermis, while lesions of the latter group are usually irregular, ill-defined with deep infiltration into the subcutaneous tissue. Besides, the presence and number of hyperechoic spots have been associated with the recurrence risk of BCC lesions. A cutoff point of 7 hyperechoic spots was used to predict a lesion attributed to low (usually <7 hyperechoic spots) versus high risk (≥7 hyperechoic spots) of recurrence [9]. Furthermore, 50 MHz ultrasound also merits detecting subclinical BCC lesions. This includes both small lesions difficult to recognize through naked eyes in the horizontal aspect and vertically deeper satellite lesions contiguous with the main tumor masses, which can be easily ignored [11]. Preoperative assessment of BCC lesions using 50 MHz HFUS can be a useful tool to define the tumor margin. However, the lesion depth measured by 50 MHz HFUS only has a moderate correlation with histopathological tumor thickness, with 50 MHz HFUS tending to overestimate the depth measurement probably due to the perilesional inflammatory infiltration [10].

HFUS at 50 MHz can also assist the differential diagnosis of BCC apart from other skin tumors. For distinguishing between BCC lesions and benign tumors such as melanocytic nevi (MN) and seborrheic keratosis (SK), it has been revealed that sonographic features of subcutaneous tissue invasion, irregular shape,

ill-defined margin, presence of anechoic area, and hyperechoic spots, as well as epidermal interrupted echo, are more common in BCC lesions. The presence and the dominant number of hyperechoic spots in BCC are previously suggested to help differentiate BCC from SCC and MM, but the feature has been found in other cutaneous neoplasms like MN, SK, and trichoepithelioma [8, 12].

Squamous Cell Carcinoma

Cutaneous SCC includes both cutaneous SCC in situ (Bowen's disease, BD) and invasive cutaneous SCC. Generally, a BD lesion is revealed as a flat or slightly elevated hypoechoic band-like structure beneath a mildly wavy epidermis (Fig. 14.3), while an invasive SCC lesion appears as a relatively heterogeneous, hypoechoic structure with an irregular border and a tendency of deep invasion (Fig. 14.4) [7, 13, 14]. A previous study carried out using 40 MHz HFUS to assess the invasive SCC preoperatively and BCC tumor dimensions found it not quite clinically useful for tumors with subclinical extension in the epidermis or subcutaneous tissue before Mohs surgery but potentially helpful to predict margins of large tumors with clinical areas greater than the median of 1.74 cm^2 and subclinical dermal involvement with acceptable accuracy [15]. Unlike BCC, SCC has a higher risk of regional invasion and metas-

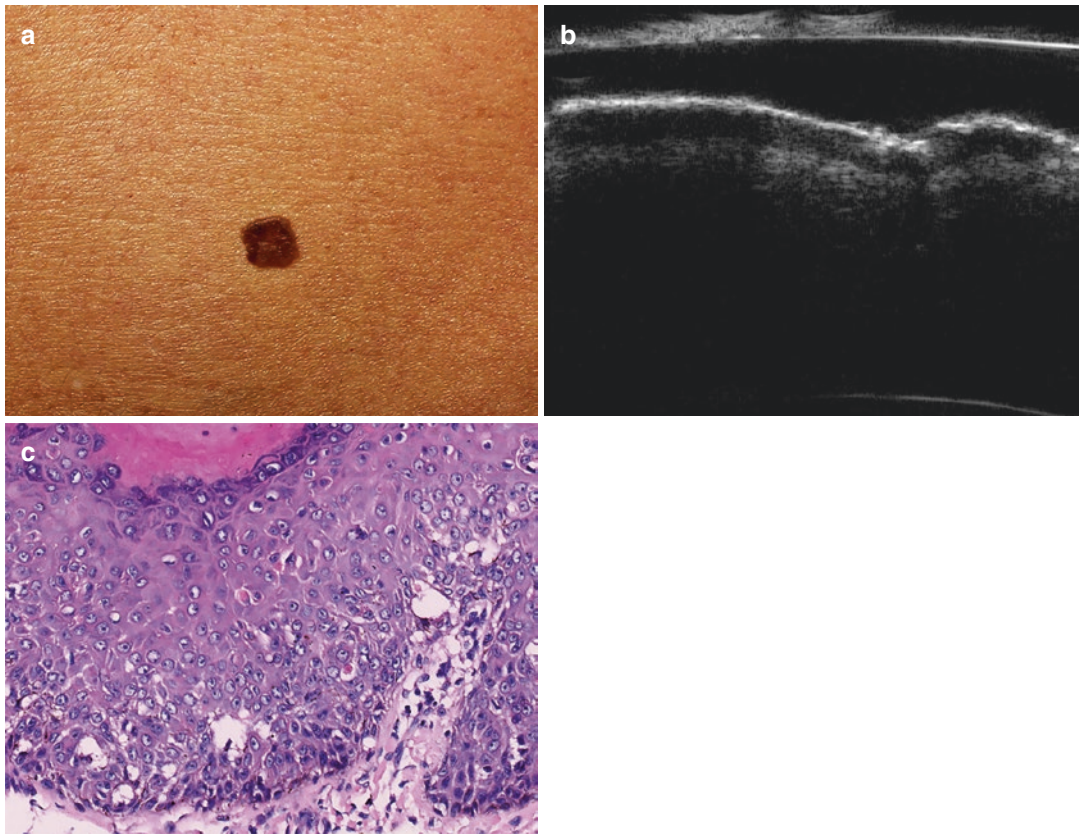

Fig. 14.3 Bowen's disease. (**a**) The clinical image shows well-defined scaly erythema on the left waist. (**b**) High-frequency ultrasound at 50 MHz reveals a superficial and homogeneous hypoechoic layer with a clear border between the slightly thickened epidermis and the underlying dermis. (**c**) Histopathologically, the epidermis is thickened with prominent dysplasia (HE, ×100)

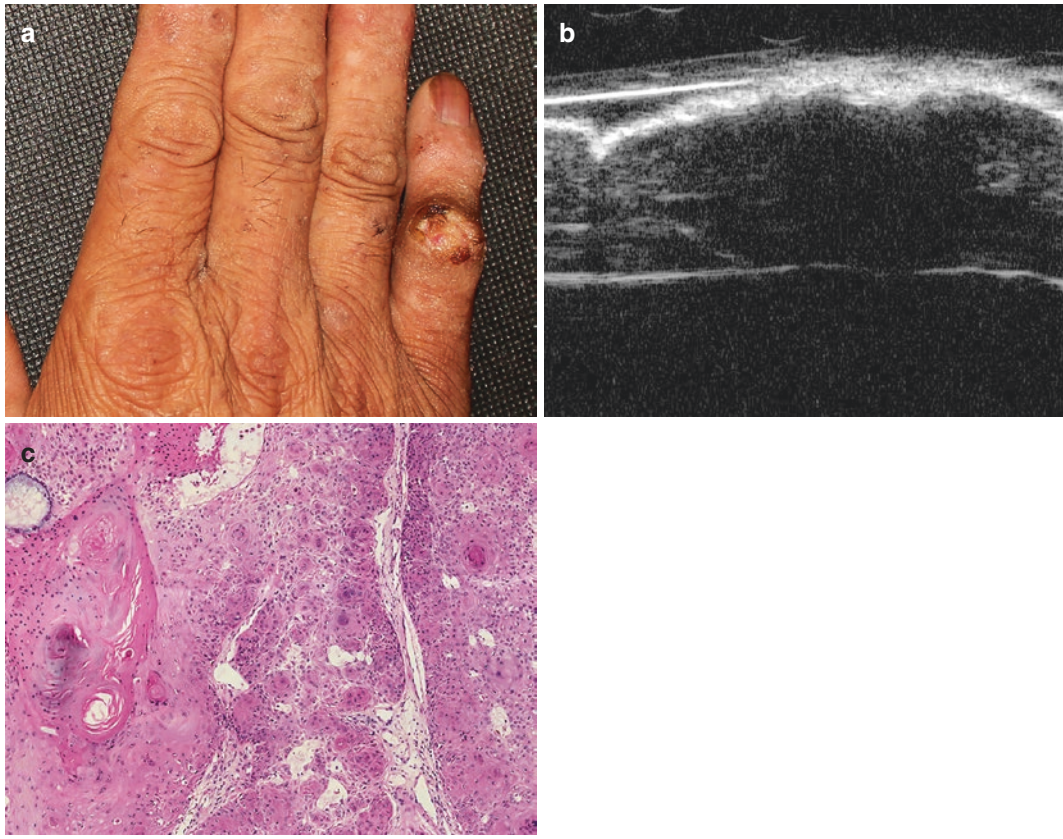

Fig. 14.4 Invasive squamous cell carcinoma. (**a**) The clinical image shows a craterlike ulcerate with central and peripheral keratinization on the finger knuckle. (**b**) High-frequency ultrasound at 50 MHz reveals an ill-defined, homogeneous, hypoechoic structure involving the dermis and subcutaneous tissue. (**c**) Histopathology shows multiple clusters of well-differentiated keratinizing tumor cells invading the dermis (HE, ×50)

tasis. Therefore, HFUS exploration into the deep dermis and subcutaneous tissue as well as locoregional lymph nodes is necessary for the assessment of SCC patients. Under this condition, superficial abnormal lymph nodes displaying large size, rounded shape with necrosis, and calcification can be easily detected by HFUS, but lymph nodes located deeper should be investigated using ultrasound with lower frequencies or combined with other imaging techniques [13].

A recent study applied 50 MHz HFUS (referred to as ultrasound biomicroscopy, UBM, in the chapter) to evaluate BD lesions [16]. They found that the most significant ultrasonic characteristic of BD is a superficial hypoechoic layer with a clear borderline between the upper epidermis and dermis, sometimes accompanied by a "wave sign." The wavy morphology of the lesion surface corresponds with keratinization stacking of the epidermis, and the well-defined and shallow hypoechoic area indicates the lesion localized within the epidermis, leaving the stratum basale intact. At the same time, a diagnosis of invasive SCC should be considered if the hypoechoic area infiltrates the dermis with thicker keratinization on the lesion surface.

Malignant Melanoma

It has been long since ultrasound was introduced in the preoperative assessment of cutaneous MM, with HFUS at 20 MHz or lower frequencies most

commonly used [17–23]. MM lesions are depicted as homogeneous hypoechoic, flat, or elliptic to fusiform-shaped structures infiltrating dermis and/or subcutaneous tissue. The hyperechoic spots are not often found inside the MM lesions (Fig. 14.5). HFUS could be helpful to estimate the tumor invasion depth and detect satellite tumors or in-transit metastases [23–25]. Furthermore, HFUS can also be useful in the sentinel lymph node localization and guide fine needle aspiration and biopsy procedures [26].

The prognosis of MM patients is greatly related to the depth of the primary lesion (Breslow's index) or the invaded skin layer (Clark's classification), and different management strategies might be considered according to these criteria along with the presence of ulceration, mitotic rate, and lymph node involvement or metastases. Previous literature has reported a moderate-to-excellent correlation between the tumor thickness measured by HFUS at 20 MHz or lower frequencies and histopathological investigation. Piłat et al. evaluated the MM thickness at both 20 and 50 MHz and compared it with the thickness values obtained in the histopathological examination. They also found a satisfactory correlation between MM measurements in the histopathological and HFUS examination. There were no statistically significant differences between 20 and 50 MHz HFUS. The HFUS underestimation or overestimation only occurred in very few cases. However, such underestima-

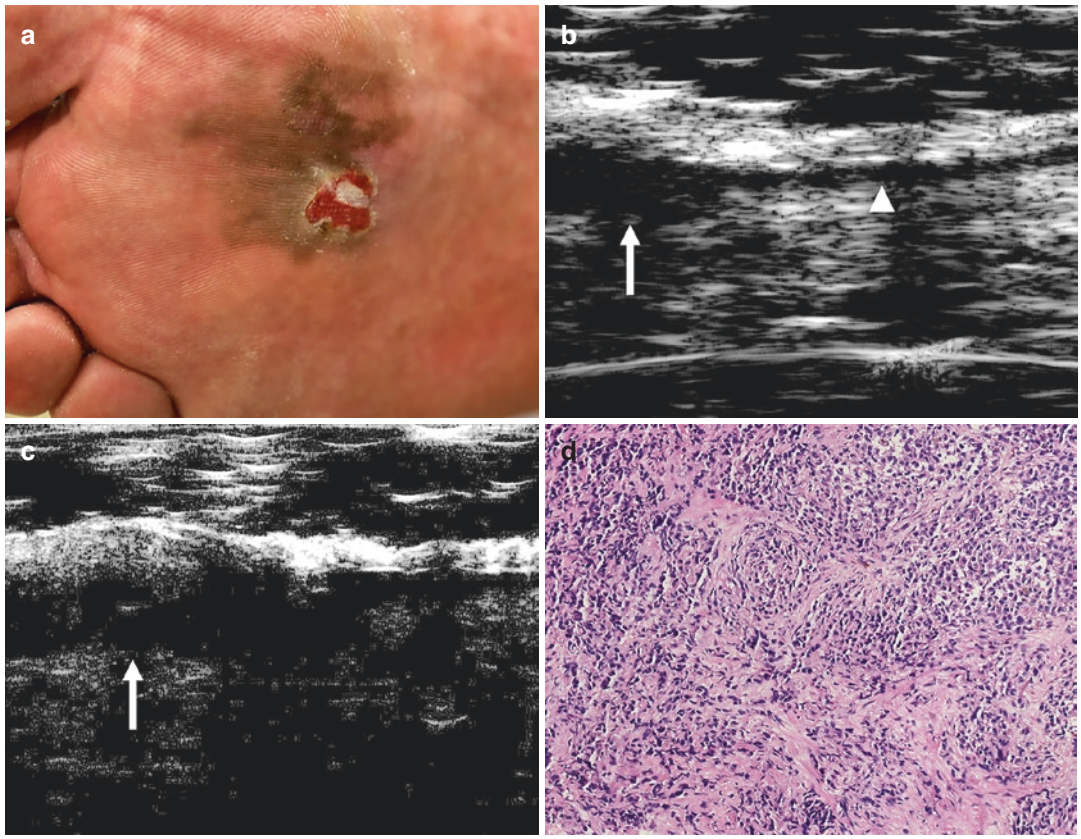

Fig. 14.5 Malignant melanoma (acral lentiginous melanoma). (**a**) The clinical image shows an asymmetric, irregular, dark-brownish blotch with ulcer formation on the sole. (**b**) High-frequency ultrasound at 20 MHz reveals a hypoechoic area (arrow) involving both dermis and subcutaneous tissue with an ill-defined boundary and homogeneous echogenicity. The normal skin adjacent (arrowhead). (**c**) High-frequency ultrasound at 50 MHz depicts tumor features (arrow) more clearly comparing with those on 20 MHz. (**d**) Histopathology shows generalized infiltration of atypical melanoma cells, sometimes arranged in nests (HE, ×100)

tion eventually had not affected the correct TNM staging of the corresponding patients, and the value differences between histopathological and sonographic evaluations were minimal. At the same time, the overestimation was speculated to be associated with inflammatory infiltration and sample shrinkage, especially for lesions located within the torso.

Primary Cutaneous Lymphoma

PCL is defined as a heterogeneous group of T-cell lymphomas and B-cell lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis [27]. Data on HFUS application of PCL is insufficient. Recent studies have been added and shown the HFUS value in assessing MF lesions [27–34]. Cutaneous B-cell lymphoma lesions are usually demonstrated as hypoechoic, multi-lobular nodules with circumscribed margins [28, 30]. MF, the most common type of cutaneous T-cell lymphoma, is characterized by the presence of a linear hypoechoic band at the junction between epidermis and dermis, which reflects the infiltration of atypical T cells, and the thickness of this band in HFUS examination has been proved to correlate well with the depth of tumor cell infiltration under histopathological examination [29, 31, 33]. Furthermore, HFUS can also quantitively monitor the treatment efficacy of MF patients during phototherapy by evaluating the decrease of SLEB thickness [29].

Owing to its higher resolution, HFUS at 50 MHz can reveal the morphological changes of MF lesions and the internal echogenicity of MF lesions in addition to the hypoechoic band and its thickness as well as layers involved [33]. Those ultrasonic parameters together are valuable in the accurate classification and staging of MF. Specifically, the epidermis of plaque lesions can be wavy, in contrast to patch lesions. An MF lesion tends to be at the early stage if the hypoechoic band has homogeneous internal echoes, confined within the dermal-epidermal junction with a regular morphology and clear boundary, while signs of the advanced stage include an irregularly shaped hypoechoic band extending to the superficial dermis or even deeper, with an ill-defined margin and inhomogeneous internal echoes. Moreover, HFUS at 50 MHz or higher frequencies seems to help in the differential diagnosis between early MF and inflammatory dermatoses like psoriasis and eczema [32, 34]. Compared with psoriasis and eczema, the epidermal an hypoechoic band d thickness of early MF lesions is lesser (with cutoff points of 0.2375 and 0.2655 mm, respectively) (Figs. 14.6 and 14.7).

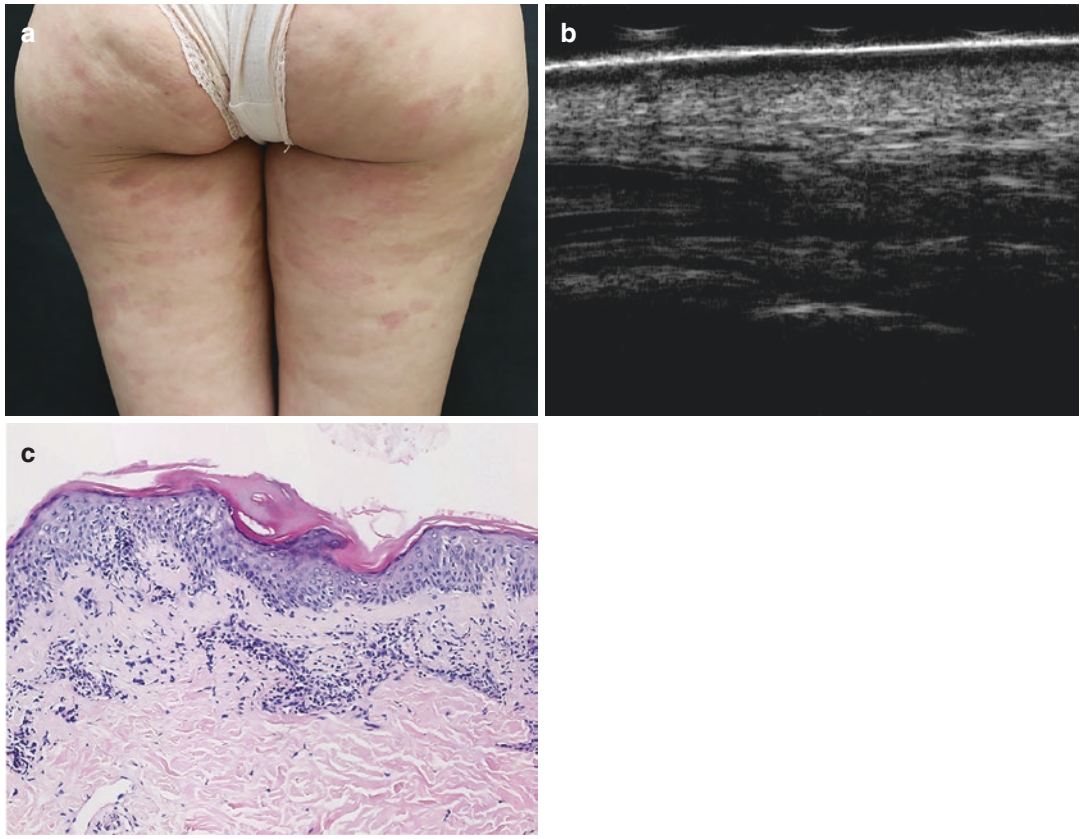

Fig. 14.6 Mycosis fungoides (patchy-stage lesion). (**a**) The clinical image shows multiple well-defined erythematous patches covered by fine scales and scattered pigmentations. (**b**) High-frequency ultrasound at 50 MHz reveals a shallow subepidermal hypoechoic band with a clear margin and homogeneous internal echoes. (**c**) Histopathology shows superficial infiltration of atypical lymphocytes with obvious epidermotropism and the formation of Pautrier's microabscesses (HE, ×100)

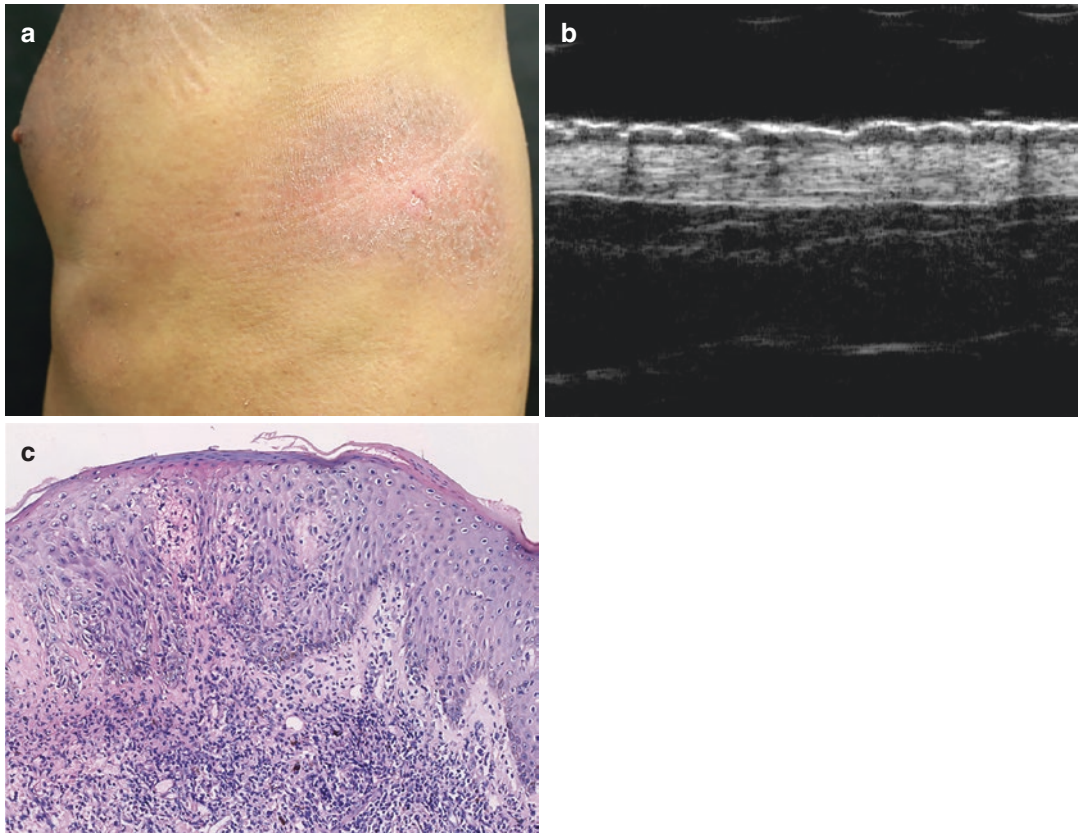

Fig. 14.7 Mycosis fungoides (plaque-stage lesion). (**a**) The clinical image shows a large and slightly atrophic plaque covered by fine scales. (**b**) High-frequency ultrasound at 50 MHz reveals a thicker subepidermal hypoechoic band, accompanied by a wavy epidermis. (**c**) Histopathology shows epidermal hyperplasia and dense infiltration of atypical lymphocytes with conspicuous epidermotropism and the formation of Pautrier's microabscesses (HE, ×100)

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