11 Ultrasound of Cutaneous Lymphomas

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Abbreviations

18FDG PET	F-18 fluorodeoxyglucose positron-emission tomography
CD	Cluster of designation
CT	Computed tomography
EBV-MCU	Epstein-Barr virus-positive mucocutaneous ulcer
EORTC	European Organisation for Research and Treatment of Cancer
HRUS	High-frequency ultrasound
IHC	Immunohistochemistry
IPI	International Prognostic Index
ISCL	International Society for Cutaneous Lymphomas
LDH	Lactate dehydrogenase
lymphomas MF	Mycosis fungoides
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
PCBCL	Primary cutaneous B-cell lymphoma
PCL	Primary cutaneous lymphoma
PCTCL	Primary cutaneous T-cell lymphoma
SES	Sézary syndrome
TNM	Tumor, node, metastases
UV light	Ultraviolet light
WHO	World Health Organization

Primary cutaneous lymphomas (PCL) are extranodal non-Hodgkin's lymphomas (NHL) characterized by the presence of malignant lymphocytes confined to the skin at the time of initial diagnosis, and for 6 months after diagnosis, without any evidence of extracutaneous disease, i.e., involvement of lymph nodes, bone marrow, or viscera at presentation, as assessed by adequate staging procedures [1, 2]. After the gastrointestinal system, the skin is the second most common site of involvement in extranodal NHL, accounting for 19% of extranodal lymphomas with an estimated annual incidence of 1:100,000 [3, 4]. Secondary cutaneous lymphomas are rare and occur when nodal or systemic malignant lymphomas involve the skin as a secondary manifestation. PCL differs significantly from secondary cutaneous lymphoma as they both display distinctly disparate genetic, clinical, histological, and immunophenotypic characteristics [1, 5, 6]. The differentiation between these two types of lymphomas is essential in their management as they have

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entirely different therapeutic approaches and treatment outcomes.

In contrast to secondary cutaneous lymphomas, which are treated by systemic chemotherapy, lesions of PCLs (unless extensive) are managed by skin-directed therapies, including UV light, topical drugs, intralesional steroids or interferon, local radiation, and surgical excision [1, 7]. In addition, PCLs exhibit a slow, indolent course and better prognosis than secondary cutaneous lymphomas [1, 8, 9]. Primary cutaneous lymphomas should also be differentiated from cutaneous dermatoses, prelymphomatous conditions, and "pseudolymphomas" occurring due to reactive lymphoid hyperplasia as these diseases resolve spontaneously after the elimination of the causative factor and symptomatic treatment.

Currently, primary cutaneous lymphomas are categorized according to the WHO classification of 2017, and an updated WHO-EORTC version of this was published in 2018. PCLs are broadly classified into two major types depending upon the cell of origin, (a) primary cutaneous T-cell lymphomas (PCTCL), accounting for about 65–75%, and (b) primary cutaneous B-cell lymphomas (PCBCL) for about 25–35% [6]. The most common T-cell lymphomas are mycosis fungoides (MF), comprising about 50% of all cases, and Sézary syndrome (SES), a rare but aggressive subtype of PCTCL. Apart from these, in the WHO classification of 2017, a new entity, Epstein-Barr virus-positive mucocutaneous ulcer (EBV-MCU), which is associated with immunosuppression, has been included [6].

PCLs are more common in middle-aged to elderly patients (mean age at diagnosis 60 years), with a female/male ratio of 0.60, and the disease is characterized by a chronic course with prolonged survival [3, 4, 10]. Epidemiological data from Europe and Asia suggests that the incidence of PCBCL has significantly increased in the last two decades, with more frequent occurrence in the older population compared to PCTCL [3, 4].

The clinical presentation of PCLs is variable, and the lesions can manifest as solitary to multiple erythematous patches, plaques, papules, acneiform lesions, nodules, and tumors [3, 6]. T-cell lymphomas frequently appear as multiple eczematous and/or erythematous plaques or as a combination of patches, plaques, and tumors in the trunk, extremities, and head and neck regions. They often show ulceration and are infrequently associated with cellulitis/panniculitis-like appearance and neoplastic lymph nodes. B-cell lymphomas appear as red-to-violaceous papules, plaques, or nodules localized preferentially to the head and neck region and extremities, especially the arms, and ulceration is uncommon [3]. Multiple lesions are more frequent in T-cell lymphomas (90%) than B-cell lymphomas (50%), which are usually limited to one body area [11, 12].

Diagnosis of primary cutaneous lymphomas is established by histopathology of the tissue obtained by fine needle aspiration or open/excision biopsy. The majority of cases occur as de novo lesions, and the lymphomatous infiltrates usually involve the dermis without any epidermotropism, often extending into the subcutaneous tissue [1, 10]. The infiltrates are mostly monomorphic (large or small cells) and are separated from the epidermis by a collagen band known as the Grenz zone [1]. The malignant lymphocytes express a specific cluster of designation (CD) markers that are used to determine the cellular lineage of cutaneous lymphomas. Immunohistochemistry (IHC) is critical in confirming the diagnosis and classification of cutaneous lymphomas into various subsets by noting the presence or absence of specific T-cell lineage markers (CD2, CD3, CD5, CD7, CD4, CD8, and CD45RO), NK cell markers (CD56), B-cell markers (CD19, CD20, CD21, CD79a, and PAX5), and other markers [13, 14]. IHC is also needed to exclude systemic lymphomas with secondary skin involvement and other cutaneous neoplasms.

Imaging studies play an important role in diagnosing, localizing, and staging cutaneous lymphomas. Though ultrasound with color Doppler is the most commonly used imaging modality, the details regarding the specific sonographic imaging features of cutaneous lymphomas are limited, which can be attributed to the rarity of this condition and the underutilization of high-resolution ultrasound (HRUS) in the evaluation of skin lesions.

The evaluation of cutaneous lesions in suspected PCL lesions is usually performed with lin-

ear array high-frequency transducers of 6–22 MHz with standardized settings; however, ultrahigh frequencies can also be used. Color Doppler and power Doppler are used to assess vascularity in all cases. HRUS examination includes a complete morphologic evaluation of lesions with a description of echogenicity, margins, measurements of transverse diameter and thickness, intralesional and perilesional vascularity, and spectral analysis wherever possible [15].

In 1997, Giovagnorio, in the first detailed study on ultrasound of primary cutaneous lymphomas, categorized their sonographic appearance as well-defined nodules (type I), polylobulated hypoechoic lesion formed by multiple nodules (type II), diffuse homogeneous hyperechoic thickening of the dermis (type III), and diffuse inhomogeneous thickening of the dermis and subcutaneous tissue (type IV) [16]. Although the study reported that focal lesions were common in B-cell lymphomas and diffuse lesions were more common in T-cell lymphomas, current studies indicate that the sonographic appearance is variable and does not always correlate with the histological diagnosis [16, 17]. In 2020, Mandava et al. described the following four types of sonographic patterns in primary cutaneous lymphomas [17]: (1) "focal infiltrative" lesions appearing as small focal dermal and subcutaneous irregular hypoechoic infiltrates (Fig. 11.1); (2) well-defined hypoechoic "nodules" (Fig. 11.2); (3) polylobulated focal hypoechoic lesions with ill-defined margins giving a "pseudonodular" appearance (Fig. 11.3);

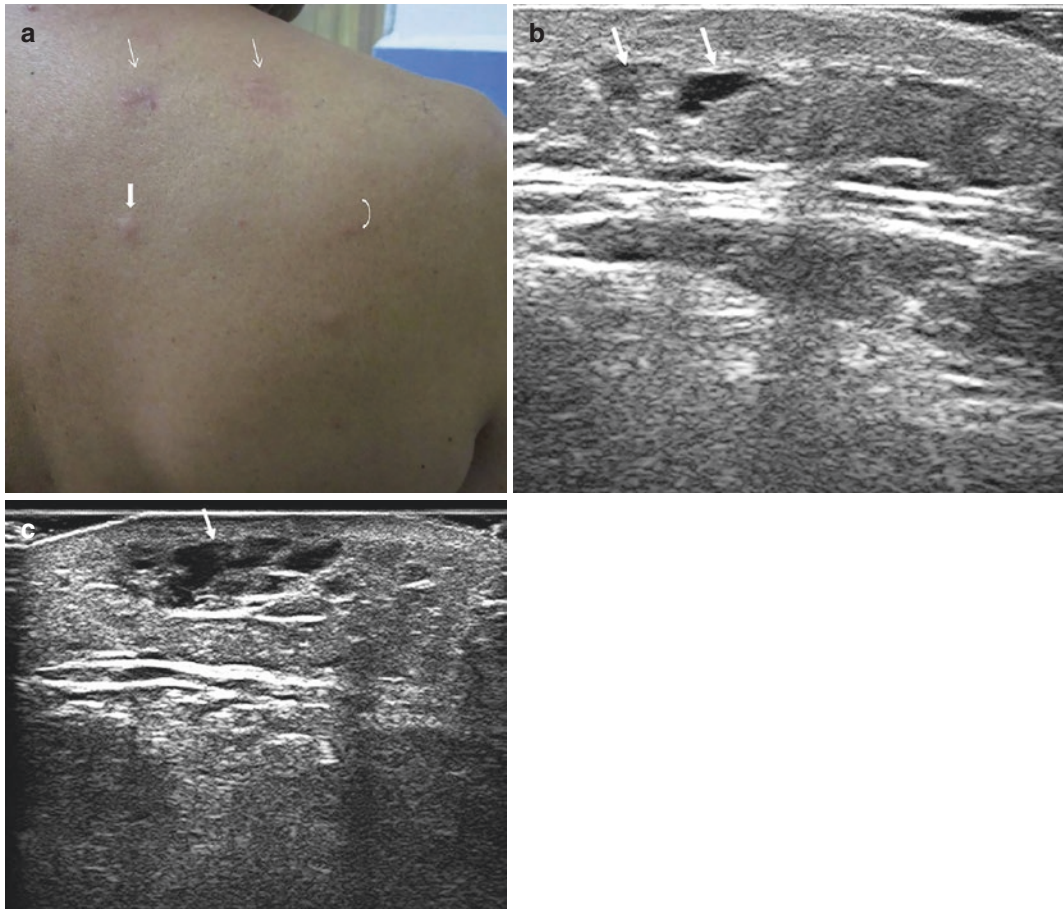

Fig. 11.1 (**a**) Clinical image of cutaneous lesions in a 61-year-old man diagnosed with primary cutaneous B-cell lymphoma shows papule (curved arrow), plaques (thin arrows), and small nodules (thick arrow) on the trunk. (**b**, **c**) HRUS image of papules present as ill-defined hypoechoic focal infiltrative lesions in the dermis and subcutaneous tissue (arrows)

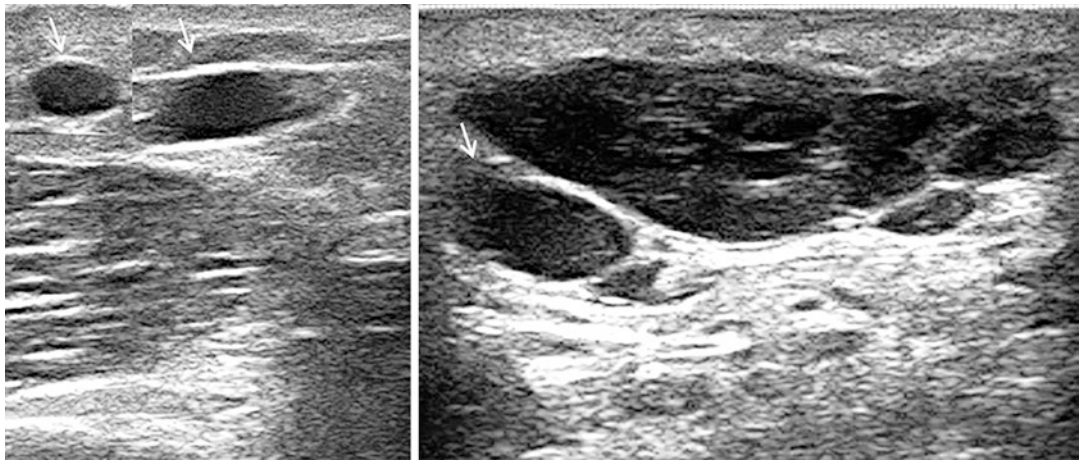

Fig. 11.2 HRUS image of cutaneous nodules demonstrates well-defined hypoechoic nodules of varying sizes in the dermis and subcutaneous tissue (arrows)

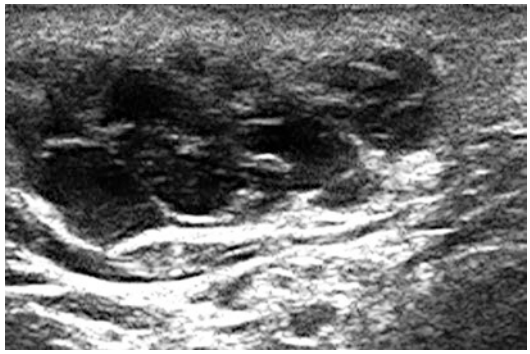

Fig. 11.3 HRUS image of cutaneous nodules shows the "pseudonodular" lesion as a polylobulated hypoechoic nodule with ill-defined margins

and (4) "diffusely infiltrative" hypoechoic panniculitis-like lesions in the dermis and subcutaneous tissue (Fig. 11.4). On HRUS, cutaneous papules appear initially as small focal dermal infiltrates, and they later coalesce to form nodular lesions and diffuse dermal infiltrates [17]. The cutaneous nodules can appear as either well-defined nodules or heterogeneously hypoechoic polylobulated pseudonodules (Fig. 11.5), and the panniculitis-like cutaneous patches and plaques are seen as diffuse heterogeneously hypoechoic

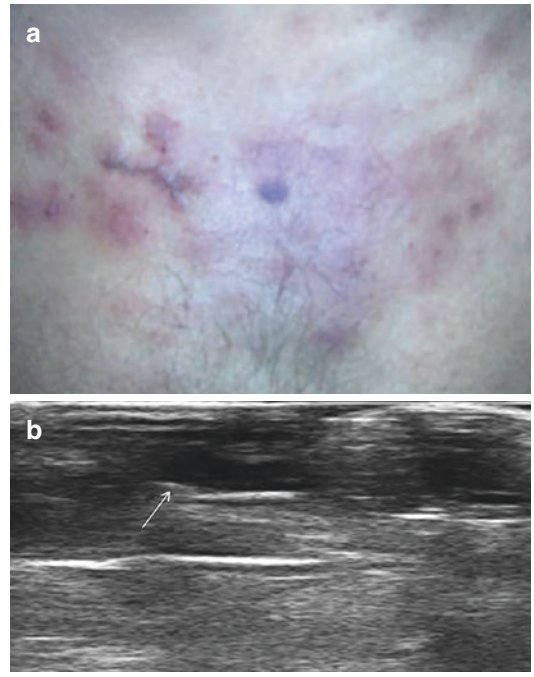

Fig. 11.4 (**a**) Primary cutaneous T-cell lymphoma: Clinical image of cutaneous lesions in a 58-year-old man presenting with erythematous patches and plaques on the chest. (**b**) HRUS image of a plaque shows heterogeneously hypoechoic diffuse infiltrative lesion with ill-defined margins in the dermis and subcutaneous tissue (arrow)

thickening of the dermis and subcutaneous tissue. Well-defined hypoechoic nodules or pseudonodules are more common in B-cell lymphomas, whereas both nodular and ill-defined hypoechoic diffusely infiltrative lesions are seen in T-cell lymphomas [17, 18] (Fig. 11.6). The lesions in PCL characteristically have infiltrative margins, and they do not exhibit any internal necrosis, calcifications, and posterior acoustic shadowing [11, 17, 18].

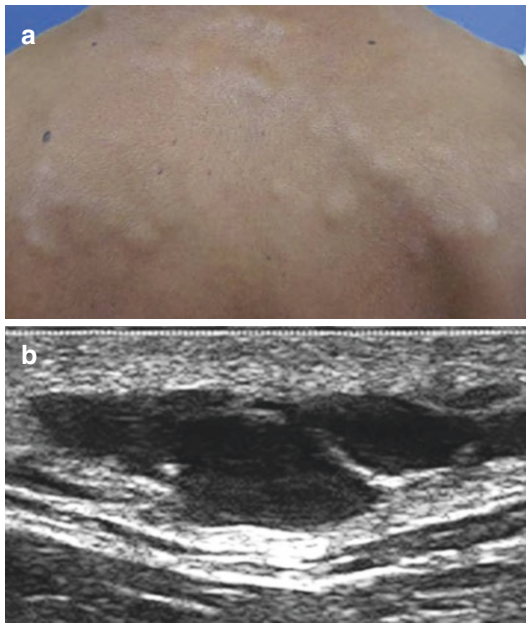

Fig. 11.5 (**a**) Clinical image of a 59-year-old man with primary cutaneous B-cell lymphoma presenting with multiple cutaneous nodules on the trunk. (**b**) HRUS image of a lesion shows a lobulated well-defined hypoechoic nodule in the dermis and subcutaneous tissue

On color Doppler examination, the initial focal infiltrative lesions are avascular to hypovascular, and as the size of the lesion increases, the nodular, pseudonodular, and diffusely infiltrative lesions exhibit vascularity, which confirms the close association between the growth of the nodules and development of internal vascularity [19] (Fig. 11.7). The spectral color Doppler analysis of the lesions display a relatively low resistive index in the intratumoral vessels compared to the normal vessels in the adjacent tissues. The lesions in primary cutaneous lymphomas are extremely vascular compared to other cutaneous and subcutaneous soft-tissue tumors, with the majority of the proliferative vessels arising from the hilum or central region [18, 20] (Fig. 11.8). Arteriovenous shunts are not seen in primary cutaneous lymphomas, unlike in other hypervascular tumors like hemangiopericytomas [18, 20].

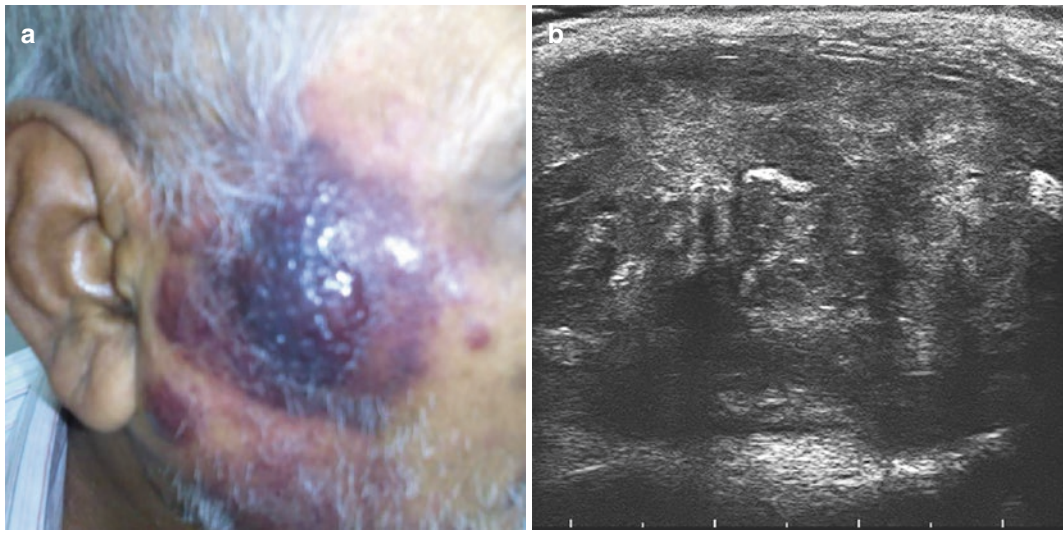

Fig. 11.6 (**a**) Clinical image of a 72-year-old man with primary cutaneous T-cell lymphoma demonstrates violaceous cutaneous nodules on the face. (**b**) HRUS image of the large nodule shows a relatively well-defined heterogeneously hypoechoic nodule in the dermis and subcutaneous tissue

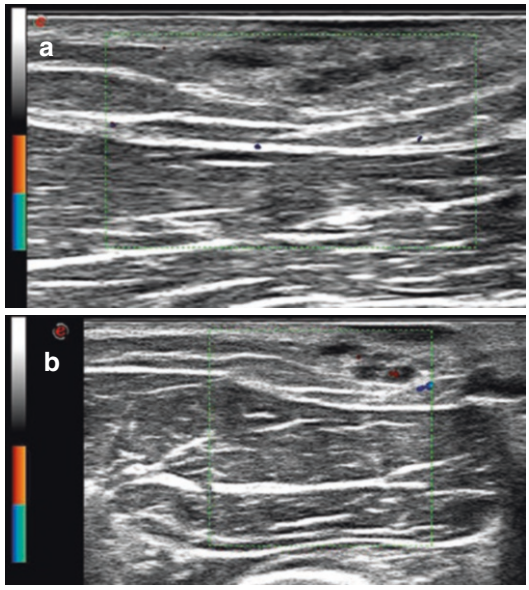

Fig. 11.7 (**a**) Color Doppler HRUS image of an initial cutaneous lesion in PBCL presenting as a small hypoechoic lesion with ill-defined margins without any internal vascularity. (**b**) Color Doppler HRUS image after 2 weeks demonstrates an enlargement of the lesion with appearance of few internal vessels

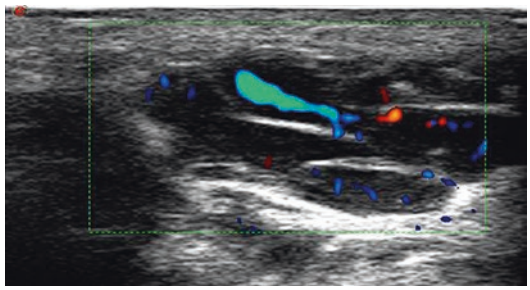

Fig. 11.8 Color Doppler HRUS image of a cutaneous nodule in a case of PBCL shows hypervascular polylobulated nodule with multiple centrally arising vessels

Though high-resolution ultrasound has a high sensitivity for the local assessment of primary cutaneous lymphomas, its specificity is too low, and therefore, histologic examination is necessary for confirming the diagnosis [11]. The other limitations of HRUS include underestimating the disease burden in multifocal tumors and its inability to depict the progression of the disease beyond the primary superficial lesions.

Radiologic demonstration of disease progression beyond the primary site is essential because the presence of extracutaneous disease and systemic dissemination leads to a drastic change in therapeutic management and significantly alters the prognosis [21, 22]. About 25% of primary cutaneous lymphomas demonstrate extracutaneous involvement at the time of diagnosis. The ISCL-EORTC-recommended TNM system staging evaluation of PCL includes a complete history, physical examination, complete blood cell examination, comprehensive serum chemistries, serum LDH, ultrasound of the neck, contrast-enhanced CT of chest and abdomen or whole-body 18FDG PET/CT, and bone marrow biopsy and aspirate [22, 23]. Most primary cutaneous lymphomas are FDG avid; hence, PET/CT is recommended for initial staging, monitoring, and post-therapeutic restaging [22, 24] (Fig. 11.9).

PCL exhibits indolent and relapsing course with frequent local recurrences, but death due to disease is rare, and the average five-year survival rate varies from 89 to 96% [9]. The morphological classification of the disease into three clinical stages according to the presence of corresponding lesions (patch, plaque, and tumor stage) has a good correlation with prognosis [25]. Cytomorphological and immunological phenotype is the most important and independent prognostic factor. Multiple lesions, lesions located on the leg, and lesions extending beyond one body area are associated with a poorer prognosis [10, 11]. According to the International Prognostic Index (IPI), which is used to assign prognosis in all subtypes of non-Hodgkin's lymphomas, the parameters predicting worse outcomes are patient age less than 60 years, elevated serum LDH, extensive regional disease (T2b), or generalized skin involvement (T3), a disease involving unfavorable body regions and biologic, molecular, and genetic markers of aggressive disease [6].

Recent studies indicate that HRUS is valuable in monitoring the therapeutic response to brachytherapy in cutaneous lymphomas, especially in mycosis fungoides [26, 27]. HRUS is also helpful in evaluating the response to treatment and the efficacy of skin-directed therapies in localized

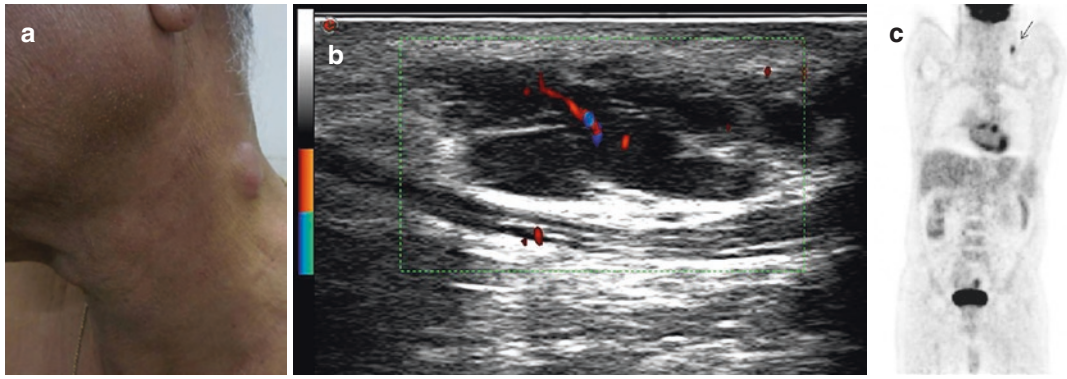

Fig. 11.9 (**a**) Clinical image of a 63-year-old man with primary cutaneous B-cell lymphoma presenting as a solitary nodule over the neck. (**b**) Color Doppler HRUS image shows a polylobulated nodule with internal vascularity. (**c**) Whole-body 18FDG-PET scan image demonstrates the hypermetabolic subcutaneous nodule (arrow) in the neck and no other lesions in the body

cutaneous lymphomas as it provides a noninvasive, repeatable, quantitative assessment of the lesions.

Conclusion

Primary cutaneous lymphoma most commonly presents as cutaneous patches, plaques, and nodules and is frequently multifocal. The clinical, cytohistological, immunophenotypic patterns and imaging features of primary cutaneous lymphomas are unique and different from cutaneous lesions secondary to nodal lymphomas and other skin cancers. PCL should always be suspected in patients presenting with rapidly growing cutaneous nodules. HRUS is valuable in the morphological assessment of PCLs and determining the extent of infiltration of lesions in the cutaneous layers. High-resolution ultrasonography suggests the diagnosis, while immunohistology confirms it, and PET/CT is the modality of choice for staging and follow-up of primary cutaneous lymphoma.

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