**Introduction**

Lipoblasts are a distinct type of mesenchymal cells that more or less recapitulate the differentiation process of normal fat. They are morphologically immature-appearing fat cells ranging from the earliest cells closely resembling fibroblasts to those having acquired lipid droplets throughout the cytoplasm [1].

According to Shaw, Todd and Bowman initially proposed in 1845 the concept that lipoblast is a specialized mesenchymal cell differing from fibroblast [2]. Wells emphasized in his review that fat cells are probably not just modified fibroblasts but are derived from units which are segregated from undifferentiated mesoderm during embryonal life and persist throughout postnatal life as specialized 'lipoblasts' [3]. Subsequently, lipoblasts were regarded as ordinarily specialized fat-forming mesenchymal cells which on occasion could produce a very wide variety of different and complex tissues [4].

Despite some morphologic overlap with embryonal fat, lipoblasts are indeed poorly identified in tissues other than those in neoplasms. In contrast, non-neoplastic, immature forms of fat cells, designated as preadipocytes or preadipose cells, are well recognized and have been extensively investigated morphologically and physiologically [5–7]. Currently, 'lipoblasts' thus refer to a range of
neoplastic immature fat cells [1].

Preadipocytes usually resemble fibroblasts and have the ability to proliferate and differentiate into mature adipocytes [8]. Although the capacity of lipoblasts to fully differentiate remains poorly assessed, they are assumed to be cellular intermediates between mesenchymal stem cells and mature adipocytes like preadipocytes. Therefore, the distinction between lipoblasts and preadipocytes is not clear, and preadipocytes may represent a normal counterpart of lipoblasts.

Since Stout described for the first time that liposarcoma is a malignant tumor of lipoblasts, the identification of lipoblasts has been overemphasized in the diagnosis of liposarcoma. It is obviously an essential task for pathologists to explore lipoblasts in some situations (i.e., liposarcomas) where their presence is crucial for proper diagnosis. However, there are many types of cells simulating lipoblasts in variable neoplastic or non-neoplastic conditions, which may create some diagnostic difficulties. In addition, lipoblasts are not only confined to liposarcoma but also appear in benign lipogenic tumors. Lipoblasts may be inappreciable or totally absent in atypical lipomatous tumor (synonymously referred to as well differentiated liposarcoma) [9]. Consequently, lipoblasts are not a prerequisite for the diagnosis of liposarcoma in the currently used diagnostic system for soft tissue and bone tumors [10].

This review describes the clinicopathologic features of a variety of neoplastic or non-neoplastic conditions with lipoblasts or their morphologic mimics in order to facilitate routine pathology practice and avoid erroneous pathologic diagnoses.

**Morphologic criteria of lipoblasts**

The morphologic criteria of lipoblasts described in the literature may vary. However, in a narrow sense, lipoblasts are the cells having hyperchromatic indented or sharply scalloped nuclei and lipid-rich mono- or multivacuolated cytoplasm [1, 11]. The intracytoplasmic vacuoles should be sharply margined, which is distinct from ill-defined vacuoles of pseudolipoblasts that contain mucin [12]. The nucleus of lipoblast may be pushed aside by a single large lipid vacuole, resulting in a signet ring configuration, or remain centrally located with small indentations by multiple small vacuoles, simulating sebaceous cells or adrenal spongiocytes [13]. In addition to the above typical lipoblasts, atypical or giant forms having large bizarre or multiple nuclei are appreciated. Such pleomorphic lipoblasts are an integral component of pleomorphic liposarcoma [14]. It should also be noted that some investigators prefer the designation of ‘atypical adipocytes’ to univacuolated lipoblasts [15].

**Histological mimics of lipoblasts**

Lipoblast-like cells are occasionally encountered in a variety of neoplastic and non-neoplastic conditions [1]. One well-known example is the adipocyte having intranuclear vacuoles (so-called Lochkern that means ‘hole in the nucleus’ in German) [16], which are visible in a histological slice grazing the nucleus of adipocyte viewed en face (Fig. 1A). Lochkern cells can be observed in benign lipogenic tumors as well as normal fat, particularly in thick sections. However, such nuclei are never hyperchromatic or pleomorphic as seen in liposarcoma.

Starvation, malnutrition or local trauma often results in atrophy of fatty tissue with lipoblast-like cells, which show reduction of intracellular lipid content and pronounced nuclei. In contrast to neoplastic lipoblasts, such atrophic fat cells are almost uniform in shape, and arranged in pre-existing lobular structures [1]. Foreign body granulomatous reactions against silicone, paraffin or other injected agents may create multivacuolated histiocytes that also simulate lipoblasts (Fig. 1B) [17, 18]. However, immunohistochemical expression of some histiocytic markers, such as Cluster of differentiation (CD) 68 and CD163, and clinical settings of patients would be helpful for leading to their correct diagnoses. It should be noted that histiocytes are also commonly positive for Mouse Double Minute 2 (MDM2) [9], which is a useful immunohistochemical marker of atypical lipomatous tumor (synonymously referred to as well differentiated liposarcoma) and dedifferentiated liposarcoma.

Multivacuolated cells resembling lipoblasts may also be recognized in brown fat or its neoplastic counterpart, hibernoma, but their nuclei are usually centrally located or slightly eccentric with often prominent nucleoli, features distinguishable from lipoblasts (Fig. 1C) [19]. Although brown fat cells or hibernoma cells express their marker protein, Uncoupling Protein 1 (UCP-1), immunohistochemically [20], lipoblasts in atypical lipo-
matous tumor/well differentiated liposarcoma may also be positive for this marker (Fig. 1D, unpublished observation). Conversely, atypical lipomatous tumor may display differentiation toward brown fat.

Pseudolipoblasts containing mucin may be present in a variety of myxoid tumors such as myxofibrosarcoma and myxoinflammatory fibroblastic sarcoma (Fig. 1E). Their distinguishing features from lipoblasts are mentioned above.

**Benign lipogenic tumors with lipoblasts**

Lipoblasts have been considered to be a histologic hallmark of malignant lipogenic tumors (i.e. liposarcomas). However, they can also be identified in benign tumors such as lipoblastoma, chondroid lipoma and spindle cell/pleomorphic lipoma. Therefore, the presence of lipoblasts alone does not warrant the diagnosis of liposarcoma.

**Lipoblastoma:** Lipoblastoma is a benign neoplasm that resembles fetal adipose tissue with a certain risk of local recurrence. Jaffe originally coined the term ‘lipoblastoma’ to describe a tumor of immature fat cells [21]. The case recorded later as lipoblastomatosis by Vellios et al. was an 8-month-old female infant with multiple subcutaneous lesions of similar morphology [22]. The tumor basically affects infants or young children who are less than 10 years old (more than 90% of cases) [23], and older or adult patients are extremely rare. According to Chung and Enzinger, tumors infiltrating into the adjacent tissue in a diffuse manner and being well circumscribed are labeled as diffuse lipoblastomatosis and lipoblastoma, respectively [24]. Microscopically, the tumor is characterized by a distinctive lobular architecture of sheets of fat cells at varying maturation stages, including primitive stellate or spindled mesenchymal cells, mono- or multivacuolated lipoblasts and mature-looking adipocytes (Fig. 1F). In contrast to liposarcomas, atypical or pleomorphic lipoblasts or stromal cells are absent. Myxoid areas and a plexiform vascular pattern are common. Immunohistochemically, the fat cells in lipoblastoma are positive for S-100 protein and CD34 [23], and desmin-positive primitive mesenchymal cells, probably of myofibroblastic phenotype, have been recently described [25]. Lipoblastoma harbors characteristic genetic alterations involving the Pleomorphic Adenoma Gene 1 (PLAG1) gene that result in fusion genes such as the Hyaluronan Synthase 2 (HAS2)-PLAG1 and Collagen type I alpha 2 (COL1A2)-PLAG1 and in over-expression of PLAG1 [26–28].

**Chondroid lipoma:** First described in 1993 by Meis and Enzinger, chondroid lipoma is a benign and extremely rare fatty tumor that is often mistaken for other neoplasms such as myxoid liposarcoma and extraskeletal myxoid chondrosarcoma [29]. The tumor mostly arises in the proximal extremities or limb girdles of middle-aged women as a slowly growing soft tissue mass. The lesion is well demarcated or encapsulated and composed of strands or nests of round tumor cells (Fig. 1G). They are often identical to mono- or multivacuolated lipoblasts and embedded in a myxochondroid or hyalinized background, displaying a lobular growth pattern. Eosinophilic vacuolated cells that resemble brown fat cells and mature adipocytes may be admixed in variable proportions. Cellular pleomorphism and mitotic activity are virtually lacking [29]. Immunohistochemically, the tumor cells express S-100 protein and sometimes CD68 [29, 30]. A recurrent chromosomal translocation, t (11; 16)(q13; p13), resulting in the chromosome 11 open reading frame 95-myocardin-like 2 (C11orf95-MKL2) fusion gene, has been recently described in chondroid lipoma [31].

**Spindle cell/pleomorphic lipoma:** Although spindle cell lipoma and pleomorphic lipoma were originally described separately [32, 33], they are currently regarded as histologic ends of the spectrum of a single entity because of their significantly overlapping clinicopathologic and cytogenetic features [34]. They usually develop as subcutaneous tumors, particularly in the posterior neck, back or shoulder of middle-aged or elderly men. Spindle cell/pleomorphic lipoma shares morphologic features with ordinary lipoma; most are between 3 and 5 cm in size and well circumscribed. Histologically, spindle cell lipoma is characterized by an admixture of mature adipocytes, small primitive or undifferentiated spindle cells and bundles of brightly eosinophilic or ropey collagen. In pleomorphic lipoma, pleomorphic giant cells having hyperchromatic or smudgy, multiple nuclei, often showing a floret-like appearance, are present together with the histology almost identical to that of spindle cell lipoma. The spindle cells and pleomorphic cells are essentially positive for CD34, immunohistochemically. Notably,
lipoblasts can be seen in some cases of spindle cell/pleomorphlic lipoma, which may make the differentiation from atypical lipomatous tumor (or well differentiated liposarcoma) difficult (Fig. 1H) [34, 35]. However, in addition to their distinct clinical settings, an immuno-histochemical or genetical assessment of recently identified markers (e.g. MDM2, cyclin-dependent kinase 4 (CDK4), p16, retinoblastoma 1 (RB1)) for each of these tumors would be helpful for the distinction between them [36, 37].

Fig. 1. Microscopic findings of a variety of lipoblasts and their histologic mimics. Lochkern cells (arrows) A, multivacuolated histiocytes (arrows) in silicone granuloma B, and multivacuolated cells in the brown fatty tissue in the adult heart C. Cytoplasmic expression of Uncoupling Protein 1 (UCP-1), a marker of brown fat, is seen in mono- or multivacuolated lipoblasts in well differentiated liposarcoma arising in the mediastinum D. Bizarre pseudolipoblasts are present in myxoinflammatory fibroblastic sarcoma E. mono- or multivacuolated lipoblasts are identified in lipoblastoma F or chondroid lipoma G. Pleomorphic lipoma may also contain lipoblasts (arrow) H.
Conclusions

Lipoblasts are abnormal or neoplastic immature-appearing fat cells with still uncertain biologic properties. In routine pathology practice, they should be differentiated from their histological mimics, including Lochkern cells, atrophic fat cells, brown fat cells, multivacuolated histiocytes and pseudolipoblasts. In addition, lipoblasts may be present in some benign lipogenic tumors or even hardly identified in atypical lipomatous tumors/well differentiated liposarcoma. Although the current diagnostic value of lipoblasts is less significant than considered previously, diagnostic lipoblasts should always be assessed based on their strict criteria with appropriate clinicopathologic backgrounds that lead to a correct diagnosis of liposarcoma.

References

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脂肪芽細胞：形態学的特徴と診断学的価値

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要 旨：脂肪芽細胞は概念的に脂肪細胞の前駆的細胞ないし未成熟な細胞であり、組織学的には脂質を含んだ単ないし多空胞状の細胞質と陥凹し、しばしば帆立貝様の濃染性核を持つことを特徴とする。主として腫瘍性疾患において見られるが、前脂肪細胞のように正常脂肪組織の分化過程をある程度再現する細胞とみなされている。伝統的にその存在は特に脂肪肉腫の診断において強調されてきたが、Lochkern細胞や褐色脂肪、偽脂肪芽細胞などの組織学的に脂肪芽細胞と類似した細胞も存在することから、病理医にとっては脂肪芽細胞の同定は必ずしも容易でない。また、脂肪芽細胞は脂肪肉腫の適切な診断のために依然として重要であるが、脂肪芽腫や軟骨様脂肪腫、紡錘細胞・多形脂肪腫といった良性脂肪性腫瘍にも認められるなどの理由で、今日の脂肪肉腫の診断における必須の条件とはなっていない。本総説では、日常の病理診断を容易にすると共に誤診の回避にも役立つように、脂肪芽細胞や脂肪芽細胞の見られる良性腫瘍および脂肪芽細胞類似細胞の臨床病理学的特徴を要約する。

キーワード：脂肪組織、脂肪芽細胞、病理診断、腫瘍。

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