INTRODUCTION

‘Avoiding pitfalls’ is not the same as ‘avoiding errors’, since errors can result from simple ignorance, technical error or incompetence. Although there are various definitions which are promulgated, the term ‘pitfall’ generally refers to unexpected or unforeseen difficulty or danger – although, as is generally well known, the original term referred to a hidden trap and a pathologist’s life seems hard enough without having to imply that specimens/slides actively seek to ensnare us! While all of us have ‘blind spots’ or areas of ignorance which may lead to misdiagnosis, in a brief overview such as this, it seems to me to make most sense to use the term ‘pitfalls’ to identify areas in which mistakes are commonly made due to unanticipated overinterpretation or else underinterpretation of specific morphologic features or immunophenotypic features which may lead to a misdiagnosis that has biologic or clinical significance. Mistaking one benign non-aggressive spindle cell neoplasm (e.g. myofibroma) for another (e.g. leiomyoma), while perhaps
regrettable or undesirable if we are seeking to do a perfect job, does not really qualify as a pitfall. Failing to recognize a rare or newly described entity represents a (generally understandable) gap in knowledge, not a pitfall. As a means of trying to validate what represents a morphologic diagnostic pitfall in soft tissue pathology, I have tried to identify the problems of this type which crop up most frequently in consultation material and a variety of examples are described briefly below.

‘WRONG’ TUMOR IN A GIVEN LOCATION

Failure to recognize that a particular morphologic pattern does not fit well with a given clinical/anatomic context or, conversely, the development of an otherwise usually easily recognized lesion at an unanticipated location can lead to a variety of often significant diagnostic problems. Examples are as follows:

**Angiolipoma**, which is usually diagnosed with ease, often seems to cause problems when arising in the breast, particularly if sampled by needle biopsy. Pathologists have a very low threshold for overinterpreting vascular lesions in the region of the breast as malignant – but important clues in angiolipoma are the absence of endothelial atypia or multilayering and the presence of distinctive microthrombi. When dealing with vascular lesions in the region of the ‘breast’ in general, it may also sometimes be helpful to understand whether the lesion was truly arising in breast parenchyma or whether instead the lesion is subcutaneous, since concern for malignancy relates mainly to parenchymal lesions.

**Myxoid liposarcoma** arises primarily in the limbs, particularly the lower limb, in the overwhelming majority of cases. Therefore, when making a diagnosis of myxoid liposarcoma at almost any other site, then the strong possibility that this might represent a metastasis from either an undisclosed or as yet undetected primary lesion in the limb should always be considered, particularly given the propensity of myxoid liposarcoma to metastasize to other soft tissue locations, very often, prior to the development of organ-based metastasis. Similarly, although liposarcoma is very common in the retroperitoneum, the large majority of such lesions are either well-differentiated or dedifferentiated and myxoid liposarcoma arising primarily at this site is very rare. However, a small but significant subset of well-differentiated liposarcomas in retroperitoneum may have a focally prominent myxoid stroma with thin-walled branching vessels and the main clue to the correct diagnosis is usually the presence of atypical spindle-shaped or
multinucleate tumor cells, not anticipated in myxoid liposarcoma. Immunostaining or FISH for MDM2 and CDK4 may also be helpful in this regard. Dedifferentiated liposarcoma may also have areas closely resembling myxofibrosarcoma but these should not be mistaken for myxoid liposarcoma which, again, very rarely shows the same degree of cytologic atypia or pleomorphism. Furthermore, the dedifferentiated areas should generally be non-lipogenic and lack lipoblasts.

**Malignant peripheral nerve sheath tumor** only very rarely arises primarily in the skin and, in that setting, is most often associated with a pre-existing neurofibroma. The large majority of cytologically atypical or malignant spindle cell neoplasms in the dermis which show positivity for S-100 protein, particularly if staining is diffuse, are in fact malignant melanomas, most often of spindle cell or desmoplastic type. Desmoplastic melanomas commonly lack any evident epidermal or junctional component, are frequently associated with a patchy lymphocytic infiltrate and may show neurotropism. Spindle cell and desmoplastic variants of melanoma are very commonly negative for second-line melanoma antigens such as HMB45 and MART-1 which may further increase the likelihood of a mistaken diagnosis of MPNST – however, melanomas show S-100 protein positivity in a much larger proportion of neoplastic cells than in most examples of MPNST.

**Fibroepithelial stromal polyp** of the vulvovaginal region is quite often mistaken for aggressive angiomyxoma, presumably because of concerns for the potentially more aggressive behaviour of the latter. However, as a simple rule of thumb, aggressive angiomyxoma almost never presents as an exophytic submucosal lesion but is almost invariably deep-seated, larger and notably more infiltrative. By contrast, stromal polyps are generally more cellular, lack any discernible margin and are characteristically exophytic. Immunohistochemistry cannot reliably distinguish between these entities.

**Sarcomas of spindle cell type**, other than the malignant mesenchymal component of a Phyllodes tumor, are extremely rare in the breast, albeit occasional such cases do occur. Nevertheless, whenever dealing with a cytologically atypical or malignant spindle cell neoplasm in the breast, in the absence of any epithelial-lined clefts to suggest Phyllodes tumor, then metaplastic (spindle cell) carcinoma is a far more likely possibility and, since any co-existent intra-ductal or invasive epithelial component is often not evident, immunostaining for several keratins and p63 will often be informative in this context.
BENIGN LESIONS WITH FREQUENTLY WORRISOME MORPHOLOGY

**Cellular benign fibrous histiocytoma** shows central necrosis in as many as 10-15% of cases and also very often extends into underlying subcutaneous adipose tissue. Neither of these features is indicative of malignancy. Attention should be paid to the mixed storiform and fascicular growth pattern, entrapment of hyaline collagen bundles and frequent overlying epidermal hyperplasia. The same guidelines are applicable to aneurysmal fibrous histiocytoma, which essentially represents cellular FH with prominent stromal hemorrhage and often increased numbers of stromal blood vessels.

**Atypical fibrous histiocytoma** (so-called ‘dermatofibroma with monster cells’) is very often mistaken for sarcoma, due to the presence of multifocally scattered large bizarre and often multinucleate cells with atypical hyperchromatic nuclei as well as mitotic figures which may be abnormal. Again, it is important to pay attention to the otherwise characteristic cytologic polymorphism of usual FH, entrapment of hyaline collagen bundles and overlying epidermal hyperplasia, as well as the clinical context which usually is that of an adult lower limb.

**Lipoma** showing extensive microscopic areas of fat necrosis is very frequently mistaken for atypical lipomatous tumor. The fat necrosis often results in marked variation in adipocyte size and the presence of histiocytes and multinucleate giant cells (some of which may be degenerate) arranged around liquefied adipocytes seems often to be mistaken for malignancy – however, such lesions entirely lack true adipocytic or stromal nuclear atypia or hyperchromasia.

**Spindle cell lipoma** quite often has a very prominent myxoid stroma and, particularly if adipocytes are few in number, then such myxoid examples can be mistaken for a variety of other tumor types. Most important among these is probably myxoid liposarcoma, since some examples of myxoid spindle cell lipoma have prominent thin-walled branching blood vessels. However, myxoid liposarcoma is extremely uncommon in the head and neck or upper back/shoulder region. Furthermore, spindle cell lipoma can be recognized by its distinctive uniform short stubby nuclei, often delicate cytoplasmic processes and ropey/refractile collagen bundles.

**Hibernoma**, when arising in the lower limb (particularly the thigh) is commonly dominated by multivacuolated lipoblast-like cells and more granular eosinophilic brown fat cells may be few in number and harder to recognize in this context – as a consequence, such lesions are often overinterpreted as atypical lipomatous/well-differentiated liposarcoma. Importantly,
however, the lipoblast-like cells usually have small central nuclei with evenly distributed chromatin, rather than the scalloped hyperchromatic nuclei of ALT.

**Lipogranulomas**, due to the introduction of exogenous lipids, most often for cosmetic purposes, seem to be increasing in frequency, given the modern obsession with physical ‘perfection’! Such lesions are easily mistaken for liposarcoma, particularly since the patient very often denies the introduction of lipid at that site. The facts that so many of the cells resemble multivacuolated lipoblasts (but lack hyperchromatic nuclei) combined with the almost invariable presence of admixed multinucleate giant cells are important diagnostic pointers.

**Plantar fibromatosis** is almost invariably hypercellular – and certainly substantially more cellular than its palmar counterpart. This hypercellularity is often mistaken for malignancy but the absence of atypia, the uniform fibroblastic/myofibroblastic morphology and the distinctively multinodular growth pattern within tendo-aponeurotic fibrous tissue are the principal clues to a benign diagnosis.

**Granular cell tumor** is only very rarely malignant and most examples of malignant granular cell tumor are large, deep-seated and show necrosis as well as significant atypia. Conversely, cutaneous granular cell tumors of ‘ordinary’ type may quite often show readily identified mitotic figures as well as mild nuclear atypia, possibly degenerative in type. In the context of a small cutaneous neoplasm showing no other atypical features, then the presence of such mitoses and nuclear alterations can safely be ignored.

**MALIGNANT LESIONS EASILY MISTAKEN AS BENIGN**

**Low-grade fibromyxoid sarcoma** is perhaps the best-known example of this potential pitfall, although these tumors are becoming more widely and reproducibly recognized since they were found to have a characteristic (7;16) translocation which can easily be detected by FISH or RT-PCR. These sarcomas usually have very bland cytomorphology, typically with a swirling growth pattern and sharply alternating fibrous and myxoid areas. Within the myxoid areas, there are frequently arcades of thin-walled blood vessels. At least 50% of these tumors are EMA positive which can easily lead to a mistaken diagnosis of soft tissue perineurioma, in which context, molecular analysis may be invaluable. Despite the very bland appearance of LGFMS, these tumors have a significant rate of distant metastasis, often after a prolonged time interval, and therefore accurate diagnosis is important.
Malignant examples of solitary fibrous tumor are often deceptively uniform in cytologic terms, since frequently they lack any significant atypia or pleomorphism. In fact, many examples show only increased cellularity in areas of the tumor, sometimes quite subtle in degree. Since the most important criterion for recognizing SFT as malignant is the identification of more than 4 mitoses per 10 HPF, then a careful mitotic count in cases of SFT, particularly if there is any evident hypercellularity, is always worthwhile. In passing, it is worth remembering that occasional examples of otherwise entirely bland and pauci-mitotic SFT may give rise to distant metastasis but this is completely unpredictable on morphologic grounds.

Low-grade myxofibrosarcoma, which usually lacks metastatic potential but which often progresses to a higher-grade lesion in any recurrence, may be easily mistaken for a benign myxoid neoplasm such as cellular myxoma. The key distinguishing feature is the presence of nuclear atypia and hyperchromasia, not generally seen in any types of benign myxomatous lesion.

MISLEADING IMMUNOHISTOCHEMICAL STAINS

Perhaps the single best example of a misleading immunostain in the setting of soft tissue neoplasia is the increasingly indiscriminate use of MIB-1 to try and determine the biologic potential of a given lesion, despite the fact that there are very limited or (more often) no reproducible peer-reviewed data to show that such staining has any predictive value in the vast majority of types of soft tissue tumor. This practice, however, cannot be labeled as a ‘pitfall’ – instead, this is simply self-inflicted foolishness!

CD34 is widely regarded as a reliable discriminant between DFSP (almost invariably positive) and cellular fibrous histiocytoma. This is, however, a mistaken belief since as many as 5% of fibrous histiocytomas, particularly the cellular variant, may show quite convincing CD34 immunopositivity. Furthermore, CD34 staining in normal non-neoplastic dermal fibroblasts adjacent to an intradermal spindle cell proliferation is often misinterpreted. In truth, H&E morphology is by far the most reliable discriminant between DFSP and cellular FH.

CD117 positivity quite often leads to desmoid fibromatosis being misinterpreted as a gastrointestinal stromal tumor (GIST). However, unless antigen retrieval is used, only a very small minority of desmoid tumors are CD117 positive. Furthermore, there are clear-cut morphologic differences between these two tumor types – in particular, the long fascicular growth pattern and collagenous stroma which characterize desmoid tumors are essentially never seen in GISTs.
**CD99** immunopositivity in a poorly differentiated or round cell neoplasm is often utilized as evidence to favor a diagnosis of Ewing sarcoma/PNET. However, a very wide variety of different soft tissue tumors may show CD99 positivity, most often cytoplasmic or focal in distribution. By contrast, Ewing sarcoma/PNET characteristically shows CD99 positivity in perhaps 80-100% of tumor cells and the staining is distinctively membranous in distribution. Cytoplasmic positivity for CD99, whether focal or diffuse, is generally non-specific and of no significance.

**Spindle cell squamous cell carcinoma**, usually arising in either sun-damaged skin or else the upper aerodigestive tract, often goes underrecognized or misdiagnosed as either atypical fibroxanthoma or else some type of sarcoma because not enough keratin stains are performed. Although the majority of examples of spindle cell SCC express high molecular weight keratins (readily detected by pan-keratin antibodies such as MNF116), a subset of cases express only lower molecular weight keratins and it is therefore advisable to stain all such lesions for pan-keratin, AE1/AE3 and CAM 5.2 in order to enhance the likelihood of accurate diagnosis. p63 is often also helpful in this regard.

**Metastatic malignant melanoma**, as is well known, may show very substantial morphologic heterogeneity and may come to resemble almost any other tumor type. It is important to remember that few tumors are so consistently strongly and diffusely positive for S-100 protein in a high proportion of the neoplastic cells and therefore, when dealing with almost any other non-distinctive malignant neoplasm showing strong S-100 positivity, melanoma should be at the top of the list of differential diagnostic possibilities. MPNST, other than when very neurofibroma-like, rarely shows such extensive S-100 protein staining. It is also important to remember that the large majority of poorly differentiated/pleomorphic and usually amelanotic metastases from melanoma will most often be entirely negative for second-line melanoma antigens. Conversely, it is also worth being aware that a small but significant subset of melanoma metastases may be immunonegative for S-100 protein but, at least in my experience, such lesions may quite often show misleading positivity for desmin (in the absence of other myogenic antigens). In a patient with an established history of malignant melanoma, this immunophenotype should not overrule a diagnosis of metastatic melanoma.

**Alveolar rhabdomyosarcoma** has been recognized in recent years to very often co-express synaptophysin and/or chromogranin. In the context of a round cell malignant
neoplasm, this can very easily give rise to confusion with a neuroendocrine carcinoma and, in my experience, this is most often a problem in tumors arising in the upper aerodigestive tract, particularly in adult patients.

**Solitary fibrous tumor** may be immunopositive for EMA in as many as 30% of cases and this can give rise to a mistaken diagnosis of synovial sarcoma. However, the patternless architecture and varying cellularity are quite different from the usual fascicular architecture of a synovial sarcoma. Furthermore, strong and diffuse positivity for CD34 is infrequent in synovial sarcomas.

**CONCLUSION**

By necessity, the examples listed above represent only a selected subset of the potential pitfalls in diagnosing soft tissue tumors. There are many additional pitfalls that arise, for example, through problems of sampling error, particularly in the era of tiny CT-guided needle biopsies. There are also a variety of pitfalls that relate specifically to histologic grading, a parameter regarded as being of the highest importance by many oncologists but which, in many cases, is determined entirely by the morphologic diagnosis. Unfortunately, it is not possible to cover the full range of diagnostic pitfalls in a brief presentation such as this.