Intramuscular high-grade myxofibrosarcoma of left buttock of 66-year-old male patient – approach to systematic histopathological reporting

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Abstract

Here we present a systematic approach to histopathological reporting of high-grade myxofibrosarcoma of 66-year-old male patient. The tumor was biopsied with fine-needle aspiration (FNA) and core-needle biopsy (CNB) and then the whole myxoid tumor was excised with left musculus glutaeus maximus. The lesion was stained with Hematoxylin–Eosin (HE), Periodic acid–Schiff (PAS), Alcian blue, Masson's trichrome, Ki67, alpha-smooth muscle actin (α-SMA), S100, CD34 and vimentin. FNA material grounded the diagnosis of non-epithelial neoplasia, while CNB was enough to produce diagnosis of myxoid sarcoma. The tumor lied under superficial fascia with no extension beyond deep fascia or any invasion of skin, vessels or nerves, either. The tumor was intramuscular, mainly myxoid with hypercellular areas of highly atypical cells with bizarre giant multinucleated cells that clearly belonged to category of high-grade sarcoma. According to Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), the case was assessed for 5 points. Ki67 index reached more than 80% malignant cells. Alcian blue was strongly positive in myxoid background. Masson's trichrome emphasized fibrillary structure of tumor. Negativity for S100, α-SMA with strong co-expression of CD34 and vimentin supported the diagnosis of myxofibrosarcoma. The lesion was diagnosed as high-grade myxofibrosarcoma (formerly myxoid malignant fibrous histiocytoma) G2 pT2b [7th edition pTNM (pathological tumor-node-metastasis), code ICD-O 8811/3 in World Health Organization (WHO) Classification 2013]. In approach to diagnosis of soft tissue malignancies, a strict sequence of procedures should be applied as only meticulous and ordered diagnostic pathway would succeed in and correct identification of a peculiar type of sarcoma.

Keywords: high-grade myxofibrosarcoma, soft tissue tumors, histochemistry, immunohistochemistry.

Introduction

Myxofibrosarcoma (MFS) is recorded as most frequent soft tissue sarcoma in elderly people with slight predominance of male patients [1, 2]. Extremities are a most frequent primary location [1, 2]. The morphology of the lesion ranged from hypocellular myxoid areas of low-grade to pleomorphic sarcoma of high-grade [3]. Distinctively, MFS is organized in nodular growth pattern; and a myxoid stroma is supplied with curvilinear capillaries and populated by fusiform, to rounded malignant cells with hyperchromasia of heterochromatin and irregularity of nuclear contours [4]. High-grade myxofibrosarcoma formerly myxoid malignant fibrous histiocytoma is quite a peculiar neoplasm that is composed of hypercellular to hypocellular fields of frankly malignant cells with fibrillar and myxomatous background containing multinucleated giant cells, high mitotic activity, and areas of necrosis [4]. In immunohistochemical panel, following stains were reported to be included: pan-keratin, S100 protein, desmin, and alpha-smooth muscle actin (α-SMA) and they were proved to be negative in case of myxofibrosarcoma [1]. Surgical removal is followed in more aggressive myxofibrosarcomas with by chemotherapy and/or radiation mostly due to high rate of local recurrences of this sarcoma [1]. Retroperitoneal and pulmonary metastases were noted in half of total examined epithelioid MFS in one study [1]. MFS component in other soft tissue tumors is rarely reported [5]. Namely there is one example of subcutaneous pleomorphic hylanizing angiectatic tumor (PHAT), a benign entity in World Health Organization (WHO) classification, which was initially designated as a sarcoma and extraordinarily recurred as a high-grade myxofibrosarcoma in case of 76-year-old woman [5].

Intratumor heterogeneity seems to be a constant feature of MFS that is best expressed in intermediate-grade tumors that comprise distinct biomolecular profiles of both high-grade and low-grade lesions [6]. Thus, such heterogeneity is consequence of tumor progression through clonal selection and is best reflected with nodular architecture of the tumor [6]. Myxoid extracellular background differs substantially on molecular level between myxofibrosarcoma and myxoid liposarcomas, even if some cases seem to present with overlapping histology [6]. Namely, tumor type and even tumor grade could present with differences of extracellular matrix in a study of myxofibrosarcomas and myxoid liposarcomas with appliance of unsupervised clustering of the biomolecular signatures [6].
High CD44s and low of CD44v6 mRNA levels were associated significantly longer survival of patients with MFS [7]. Cell cycle state markers such as minichromosome maintenance protein 2 (MCM2) and Ki67 were evaluated in 51 cases of myxofibrosarcomas to reveal higher MCM2 expression than Ki67 labeling [8]. MCM2 was inversely correlated with the time to first recurrence [8]. Recently, Akt/mammalian target of rapamycin (mTOR) pathway has been found to be involved in the growth of MFS with evident association with histological grade and tumor progression of primary and recurrent tumors, as molecular components of that pathway Akt, mTOR, S6 ribosomal protein, 4E-binding protein, and mitogen-activated protein kinase 1/2 were activated via phosphorylation at rates from 42.6% to 64.7%, of 68 studied MFS [9].

Although recent studies added a lot in understanding the biology of MFS, here we focused more at presentation of a point by point a systematic and detailed pattern of histopathological reporting of such a lesion on example of intramuscular high-grade myxofibrosarcoma of left buttock of 66-year-old male patient.

**Case report**

The patient was admitted to the Department of Surgery because of a reasonably large tumor of left buttock that was caused discomfort in every day physical activity of the patient and paresthesias of left lower limb. The patient did not consulted medical specialist previously because of the tumor and at last, he agreed for surgical resection of the tumor. No physiological and pathological antecedents and heredocollateral antecedents were reported. The skin area was elevated over tumor at the left buttock and a bit tender during palpation. There was no essential abnormalities in subsequent clinical laboratory tests.

The tumor was biopsied with fine-needle aspiration (FNA) and core-needle biopsy (CNB). The FNA material comprised of moderately atypical elongated fusiform cells and some epithelioid cells giving an impression of non-epithelial tumor but it was not enough to confirm its malignant nature. Subsequently, CNB was preformed to clearly state malignant nature of the lesion with a diagnosis of "myxoid sarcoma". FNA material grounded the diagnosis non-epithelial, spindle cell neoplasia, while CNB material was consistent with S100 negative myxoid sarcoma (Figure 1A).

Following CNB diagnosis, the whole myxoid tumor was excised with skeletal muscle of left buttock partially covered with fascia. The postoperative material was sent with label tumor of left buttock to the Laboratory of Pathology. The material comprised a 19×16×9 cm large muscular tissue partially covered with fascia and with 16×5 cm large skin. On cut surface, there was an intramuscular, quite well demarcated from brownish muscular tissue, pale gray, myxoid, gelatinous, multinodular 9 cm in diameter tumor of partially fragile consistency with yellowish 2.5 cm in diameter intratumoral area. The neoplasm thoroughly infiltrated surrounding tissue. Macroscopic margins seemed to be uninvolved by tumor and the surgical section surface of fascia was smooth while surfaces of margins were a bit rough.

The lesion was postoperatively stained with Hematoxylin–Eosin (HE) (Figures 1 and 2). The tumor was located inside the skeletal muscle deep under superficial fascia that faced a skin area. Under inspection, tumor did not extend fascia at deep margin and did not invaded skin and subcutaneous adipose tissue with no infiltration of vessels and nerves, either. Thus excision was reported to be complete with one minimal margin up to 1.5 mm R0 (macroscopically complete resection with negativity of microscopic margins). The tumor was mainly myxoid with hypercellular areas of densely packed highly atypical cells with giant multinucleated scattered cells of striking atypia that clearly belonged to category constituting high-grade sarcoma (Figures 1B and 2, A–C). The lesion mainly presented as myxofibrosarcoma of intermediate grade, though. Characteristically, fusiform malignant cells were arranged in laces in hypocellular myxoid areas. Fields of greater cellularity were composed of interlacing thicker and thinner fascicles of frankly malignant cells with hyperchromatic and irregular nuclei streamed into a storiform pattern. In myxoid areas, the cells were elongated, while when densely packed, the cells acquired oval shapes with eosinophilic cytoplasm but unclear cell margins that sometimes made the cell shape difficult to define.

**Figure 1** – Tissue architecture of myxofibrosarcoma (HE staining): (A) Myxofibrosarcoma core biopsy sample (×100); (B) Interface between hypercellular high-grade area and myxoid hypocellular component of MFS (×100).
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Figure 1 (continued) – Tissue architecture of myxofibrosarcoma (HE staining): (C) Inter-lacing fascicles of loosely arranged, elongated fusiform malignant cells (×200); (D) Spindled malignant cells (×400).

Figure 2 – Cytological hallmarks of malignancy in myxofibrosarcoma: (A) Striking atypia of malignant cells in hypercellular MFH-like sarcomatous areas (HE staining, ×200); (B) Mitotic figures dispersed among malignant cells with nuclear heterochromatin pattern (HE staining, ×400); (C) Occasional striking atypia of some malignant cells in hypocellular fields of MFS (HE staining, ×400); (D) Intense Ki67 nuclear immunoreactivity of sarcomatous cells (Ki67 immunostaining, ×400).

A selected tissue sample was stained with PAS to look for neutral mucins and with standard Alcian blue – pH 2.5 to search for presences of acidic mucins (Figure 3A). As golden standard Masson’s trichrome (++) staining was performed (Figure 3B). A panel of immunohistochemical stainings included Ki67, α-SMA, S100, vimentin (Figure 3C) and CD34 (Figure 3D). According to Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), the case was assessed for 5 points: 1 (necrosis occupied approximately 25% of tumor area being much less than...
50% of examined tumor fields) + 2 (histopathological tumor type – myxofibrosarcoma) + 2 (mitotic activity it was varying depending on cellularity of examined areas but it was assessed in so-called “hot spots”). Ki67 index reached over 70% of malignant cells (Figure 2D). Alcian blue was strongly positive in myxoid background. Green-blue reaction in Masson’s trichrome staining emphasized fibrillary structure of tumor. Negativity for S100 and α-SMA were additional aids to exclude a variety of soft tissue malignancies. Strong co-expression of CD34 and vimentin supported the given diagnosis of myxofibrosarcoma (Figure 3, B and C).

The lesion was diagnosed: high-grade myxofibrosarcoma (myxoid malignant fibrous histiocytoma) G2 pT2b (according to 7th edition pTNM), code ICD-O 8811/3 (according to WHO Classification 2013). The post-surgery evolution included adjuvant radiation therapy of post-operation area.

Discussion

Although limbs are favored location for MFS [10], the reliable incidence of this type of tumors at buttock level is obscure as local registry data are not quite representative for the worldwide incidence of MFS.

The metastagenicity of the MFS strictly depends on its grade as only intermediate and high-grade neoplasms were reported to give metastases [4]. It is multinodular and infiltrative with subcutaneous location but it can invade the overlying dermis with potential pitfall in differential diagnosis of CD34-positive cutaneous tumors [3].

In distal location, myxofibrosarcoma recurred less frequent than leiomyosarcoma (LMS) in spite of the fact that myxofibrosarcomas were more often deep-seated and of larger diameter than 5 cm in comparison to LMS [11]. Radioresistance of MFS was questioned due to high rate of local recurrences but radiation therapy in MFS was found to be clinical advantage [11]. In slight difference from usual high-grade MFS, some subtypes of high-grade MFS like epithelioid MFS showed relatively quickly 70% local recurrence rate and 50% of studied cases gave metastases. Due to multiple local recurrences, MFS has a quite poor prognosis with 96 months of a median survival and 65% of four-year overall survival (OS) [12].

The described by us MFS was classically diagnosed in 66-year old patient which was typically reported to be median age for MFS in analysis of 75 patients by Mentzel et al. [4]. Clinically, our case was larger size than 5 cm and was deeply seated lesion. It was of high histological

Figure 3 – Histochemical and immunohistochemical profile of myxofibrosarcoma: (A) Alcian blue diffusely positive staining for presence of acidic mucins in myxoid matrix of MFS (PAS/Alcian blue staining, ×400); (B) Blue green staining with favoring rather fibrous component rather than myogenic one appliance of Masson’s trichrome method (×400); (C) Vimentin positive staining of MFS (Vimentin immunostaining, ×100); (D) Strong cytoplasmic immuno-reactivity to CD34 of malignant cells (CD34 immunostaining, ×100).
grade (grade 2 according to FNCLCC), so it presented with the poor prognostic factors, which were associated with significantly decreased survival in analysis of 45 MFS [13]. Over 70% of malignant tumor cells of our MFS presented with positive nuclear Ki67 staining to note that high mitotic rate and high MB-1 labeling index (LI) were proved to harbor ominous prognosis in the study of Oda et al. [13].

In our opinion, the golden standard of diagnosis of any sarcoma should include FNA, core biopsy and post-operative histopathological report after complete surgical removal of the tumor. Cytological material that is obtained via FNA, has of course its limitations for establishment of precise diagnosis but FNA should never be discouraged and should be a recommended first step of pathological diagnostic pathway. As in our case, FNA is usually sufficient to establish neoplastic character of biopsied mass, but it was also reported to be useful to reveal of the myxoid background, define spindled nature of the lesion or efficient to record large, pleomorphic, and hyperchromatic nuclei [14]. In our case, firstly FNA was preformed with diagnostic conclusion of non epithelial neoplasm which is accord with findings of Olson & Ali who stated that FNA material is not sufficient for firm diagnosis of MFS even if there is cytomorphology of high-grade sarcoma cells or myoid matrix in cytological smears [15]. However, cytological report of case was cautious and limited only to diagnosis of fusocellular neoplasm as, FNA cytomorphology of high-grade myxofibrosarcoma overlaps with other adult pleomorphic sarcomas [14].

Chromatin was coarsely granular in nuclei mostly presenting heterochromatin pattern in our case (Figure 3, B and C). Although nuclei tended to be rounded in hypercellular areas, they occurred very frequently to present with irregularity of nuclear contour. In addition, cytoplasm was elongated to constitute a fusiform shape with filamentary appearance in our case. As rare epithelioid variant of MFS is characterized with round nuclei, vesicular pattern of chromatin, nuclear prominence and moderate quantity of eosinophilic cytoplasm [1]. Our case presented with multinodular, invading growth with of solid and myxoid fields of alternating cellularity from hypercellular areas and hypocellular ones similarly to findings of Nascimento et al. [1]. CD34 immunoreactivity which is also found in low-fat/fat-free’ spindle cell/pleomorphic lipoma, could lead to diagnostic pitfall in low-grade myxofibrosarcomas [12]. However, coexistent S100 negativity could prevent misleading diagnosis and could help to settle a right diagnosis of myxofibrosarcoma as in our case. In accord to study of Smith et al., we characteristically noted the same strong staining of cytoplasm within cellular processes in MFS cells [16]. Coexpression of vimentin and CD34 is confirmative – in the context of presence of described morphology – for diagnosis of MFS in our case. Such a co-expression seems to be a quite characteristic for MFS even with rare locations of such a tumor [17, 18]. Namely, pediatric intracerebral primary low-grade myxofibrosarcoma showed such a co-expression without any rearrangements of FUS and EWSR1 gene in subsequent fluorescence in situ hybridization (FISH) protocol [17]. Due to limited significance of such molecular testing, we gave up idea of its appliance in our case.

In differential diagnosis, we excluded myxoid liposarcoma mostly due to lack of lack of lipoblasts, S100 negativity and great cellularity of most areas. Although macroscopic view suggested diagnosis of jelly-like, gelatinous tumor, a great level of sarcomatous atypia contradicted intramuscular myxoma, aggressive angiomyxoma and cellular myxoma diagnosis. α-SMA negativity discouraged diagnosis of any sarcoma of myogenic nature. Desmoid fibromatosis, inflammatory myxohyaline tumor of distal extremities, myoid desmofibrosarcoma, proliferative fasciitis, and cell fibrolasitosa could present morphological appearances of fibrous or at least partially hyalinized lesions of variegated cellularity in hardly few details in common with our case of high-grade myxofibrosarcoma that could be easily distinguished from them by presence of numerous atypical mitotic figures and extraordinary high Ki67 index that extended 70% of sarcomatous cells. High-grade myxofibrosarcoma is indeed a tumor of distinct macroscopic and microscopic appearance with immunoprofile, which is specific enough to surely confirm the diagnosis.

We do think that giving the correct name for the tumor alone is far unsatisfactory, if some diagnostic protocol issues are neglected. Therefore, it is mandatory to include an applied grading system of soft tissue tumors in every histopathological report. We established a diagnosis of high-grade myxofibrosarcoma according to modified FNCLCC grading system as in example of another one high-grade myxofibrosarcoma located in right upper arm [19]. In our opinion, such an inclusion of detailed classification should be a rule of every complete report of such a tumor because it is widely used in case of grading of myxofibrosarcoma [20]. Of course, intermediate and high-grade grades of MFS are viewed to be associated with higher risk of local recurrence [12]. Moreover, besides high-grade morphology, epithelioid variant of MFS is a predictor of metastasis in course of MFS [1]. However, staging seems to be more important than grading and any histopathological variant in this kind of tumor as it was reported that subcutaneous low-grade lesions are characterized with far much better prognosis than deeply seated high-grade tumors [20]. In addition, if low-grade MFS exceeds diameter of 5 cm and contains areas of necrosis, it follows more ominous course with higher risk of metastasis [20]. Stating if the resection is complete is also indispensable in histopathological because MFS are prone to recur locally if the resection margins are close or positive [10].

Conclusions

Myxofibrosarcoma is an example of the tumor, whose, correct laconic diagnosis tells little about prognosis in each individual case, if it is not associated with defining of resection margins clearance, grading and staging. That is why, ordered histopathological report of such a soft tissue malignancy is so important for medical practice. Sharing such an opinion in this approach to diagnosis of myxofibrosarcoma, our aim was to emphasize a strict sequence of procedures that should be applied, because only a meticulous and ordered, diagnostic pathway would succeed not only in correct identification of a peculiar type of sarcoma but would be of clinical benefit, if other
indispensable points of histopathological report are not abandoned.

Conflict of interests
The authors declare that they have no conflict of interests.

References


