Dedifferentiated Liposarcoma of the Deep (Paralaryngeal) Soft Tissue: Lessons Learnt from a Case with a Partly Deceptively Benign Appearing Dedifferentiated Component

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Abstract We present a case (female, 61 years of age) of dedifferentiated liposarcoma of the deep, cervical (paralaryngeal) soft tissue with a significant myxoid component and characteristic immunohistochemical (strong and diffuse expression of p16, mdm2 and cdk4 in both the well differentiated liposarcomatous and dedifferentiated components) and molecular genetic findings (*MDM2*-gene amplification on fluorescence in situ hybridization). The myxoid component which was present in the well differentiated liposarcomatous component gave the tumor atypical radiological features. The case presented initial diagnostic difficulties, mainly because of the bland histomorphological appearance of the limited biopsy material from the sampled non-lipogenic, dedifferentiated component. The dedifferentiated part of the tumor turned out to harbor significant heterogeneity with regards to cellularity, cytomorphology and proliferative activity.

Keywords Liposarcoma · Dedifferentiated · Larynx · MDM2 · CDK4 · p16

Introduction

Dedifferentiated liposarcoma (DDLs) has traditionally been defined as a neoplasm composed of a combination of an

alipogenic sarcoma and a well differentiated liposarcoma [1]. DDLs occur over a wide age spectrum, but the tumor is most commonly diagnosed in older adults (>50 years of age) and with a significant more common occurrence in men. Almost half the cases are located in the retroperitoneum with the thigh, scrotal and groin areas being relatively common locations [2–4]. DDLs of the head and neck region is rare, accounting for only a few percent of the total number of cases. Most commonly dedifferentiation is present at the time of diagnosis, but in a significant minority of cases (approximately 10 %), the dedifferentiated component is first detected in a recurrence. Herein we report a case of DDLs of the deep (paralaryngeal) soft tissue which on a limited biopsy specimen showed deceptively bland histopathological features.

Case Report

A 61 year old Chinese female sought medical attention because of a vague sensation of a “lump in the throat” on her left side upon swallowing, of about 1 month duration. There were no associated symptoms of reflux or dysphagia. Her medical conditions of diabetes mellitus, hypertension and hypercholesterolaemia were well controlled.

Clinical examination, including a flexible fiberoptic endoscopic examination, revealed a distinct bulge at the left peri-arytenoid location, adjacent to the entrance to the left piriform fossa. The overlying mucosa was normal, suggesting an extrinsic mass pushing inwards. Palpation of the neck did not reveal any abnormal masses or enlarged lymph nodes.

Radiological examination (magnetic resonance imaging; MRI) demonstrated a fairly well circumscribed lobulated, complex solid left paralaryngeal mass measuring 3 × 3 × 5 cm, located between the inferior constrictor muscle and the

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pharyngo-laryngeal mucosa. The tumor extended inferiorly from the hyoid bone, indenting on the upper pole of the left thyroid lobe (Fig. 1). The tumor extended into the left laryngo-pharyngeal space, anterior to the left common carotid artery and was located deep to the left anterior strap and sternocleidomastoid muscles. The centro-medial component of the mass was heterogeneously contrast enhancing. A CT guided biopsy was performed.

The patient subsequently underwent a surgical removal of the mass, with an uneventful post-operative recovery. The intraoperative findings were those of a 6×3 cm bosselated, encapsulated tumor with the deeper (more solid) component projecting medially into the left piriform fossa and enveloped between the pharyngeal mucosa and the inferior constrictor muscle layers. The softer (yellowish) component of the tumor extended inferiorly to the superior pole of the left lobe of the thyroid gland, and was seen to be separate from the thyroid gland itself. The left superior parathyroid gland was identified and preserved.

After the diagnosis was established, the patient underwent a whole body positron emission tomography (PET)-scan which revealed no other tumors elsewhere. In view of the final histopathology report, the patient was referred for postoperative adjuvant radiotherapy which she is currently undergoing.

Materials and Methods

The tissue was fixed in formalin, embedded in paraffin and $4 \mu\text{m}$ thin sections were cut and stained with hematoxylin

Fig. 1 Contrast enhanced MRI revealed a well circumscribed lobulated, paralaryngeal mass (arrows) with heterogenous contrast enhancement. The (medial) dedifferentiated component exhibited stronger enhancement

and eosin (H & E). An immunohistochemical study was performed using commercially available antibodies to the following antigens according to the protocols of the manufacturers': S100-protein, smooth muscle actin (SMA), epithelial membrane antigen (EMA) h-caldesmon, low molecular weight cytokeratins (Cam 5.2), cytokeratin 7, desmin, CD34, mdm2, cdk4, Ki-67 and p16. Fluorescence in situ hybridization (FISH) for detection of *MDM2*-gene amplification was performed.

Results

Biopsy: Small fragments of lesional tissue were identified. This was composed of spindled cells with bland, monomorphic, round to oval nuclei and indistinct, vaguely eosinophilic to clear cytoplasm with no mitotic activity detected (as was later seen in parts of the resected specimen).

Resected Specimen

Gross Pathology

The resected specimen was that of an elongated, bilobulated, asymmetrically, hourglass-shaped, tumor measuring $5.5 \times 2.5 \times 1.5$ cm. The larger lobe measured $3.5 \times 2.5 \times 1.5$ cm and the smaller lobe $2 \times 2.5 \times 1.5$ cm. The outer surface was mostly smooth. The cut sections of the smaller lobe showed a well circumscribed tumor with relatively firm, solid, white–grey appearance. The cut surfaces of the larger lobe also showed a well circumscribed tumor with soft consistency and focally yellowish color with white streaks. No cystic or necrotic areas were identified.

Histopathology

The larger (grossly soft and focally yellowish) lobe was predominantly composed of relatively hypocellular, myxoid and fibrous areas intermingled with variably sized lipocytic areas and scattered lymphoid aggregates. A significant part of this part of the tumor was almost completely myxoid (Fig. 2a). The lipocytic component contained some vacuolated cells with focal nuclear indentations, i.e. features of lipoblasts. Variation of nuclear size and focal hyperchromasia of the lipocytes were present. Also the spindle cells in the fibromyxoid/fibrosclerotic areas showed focal nuclear enlargement and hyperchromasia corresponding to “atypical stromal cells” (Fig. 2b).

The smaller (grossly firm, solid white–grey) nodule was composed of a alipogenic, neoplastic spindle cell component featuring prominent variability in cellularity (Fig. 3a). Multiple aggregates of lymphoid cells mainly, but not

exclusively, located to the periphery of the tumor were present. The less cellular and cellular areas were intimately intermingled and the former were composed of spindle cells with bland nuclear features (Fig. 3b, c), myxoid extracellular substance and a vascular component of small caliber vessels while the latter (cellular) areas were composed of spindly to round cells with frequently overlapping nuclei, arranged in short fascicles and sheets (Fig. 3d). The cells in these distinctly more cellular areas had hyperchromatic nuclei with irregular nuclear membranes and small to inconspicuous nucleoli. The mitotic activity varied significantly between the hypo- and the hypercellular areas; only occasional mitotic figures were identified in the less cellular areas whereas mitotic figures were readily seen in the cellular parts. There was no necrosis. The spindle cell component was surrounded by a fibrous (pseudo-)capsule where the margin was not involved by neoplastic cells. The other nodule (with atypical adipocytic features) displayed focal involvement of the margin.

Immunohistochemistry

Alipogenic component: The neoplastic cells showed mostly weak and focal expression of S100-protein, smooth muscle actin, EMA and h-caldesmon. No expression of cytokeratins (Cam 5.2. and CK7), desmin or CD34 was detected. The proliferative activity (Mib-1/Ki-67) displayed pronounced variability; the hypocellular areas with bland neoplastic cells showed low proliferation whereas most (but not all) of the hypercellular areas displayed significant proliferation of approximately 20–30 % in the most active areas.

Both the adipocytic (well differentiated liposarcomatous) and alipogenic components exhibited strong nuclear and cytoplasmic expression of p16 (data not shown), mdm2 (Fig. 4a, b) and cdk4 (Fig. 4c, d).

After the work up of the resected specimen, we went back to the biopsy and performed a limited immunohistochemical

study (p16, mdm2 and cdk4) on this and there was strong expression of all these markers.

FISH

All of the 60 tumor cell nuclei of the non-lipogenic component that was scored showed amplification of the *MDM2*-gene (at 12q15) with a ratio of MDM2 to CEP12 signals of 10.5.

Discussion

The concept of dedifferentiation in relation to liposarcoma was introduced by Evans in 1979 [1] and the diagnosis has traditionally required the presence of an alipogenic sarcoma either juxtaposed to a well differentiated liposarcoma (WDLS) or in a recurrent WDLS. The dedifferentiated (alipogenic) component may constitute a minimal to overwhelming majority of the tumor volume and high-grade variants commonly display gross necrosis and a variegated (gross) appearance in contrast to low-grade variants which typically are more uniform and do not show evidence of necrosis. The histologic appearance of the dedifferentiated component is highly variable and include morphological patterns that may be encountered in (so called) malignant fibrous histiocytoma, myxofibrosarcoma, fibrosarcoma, but also with examples showing a hemangipericytomatous morphology and some cases may show histologic features overlapping with gastrointestinal stromal tumors. Heterologous differentiation, including osteosarcomatous, chondrosarcomatous, leiomyosarcomatous and rhabdomyosarcomatous morphology may occur. The latter may reveal itself only on an immunohistochemical level. Rarely, DDLS may display a paraganglioma-like histologic pattern [5], angiosarcomatous differentiation [6] or inflammatory myofibroblastic tumor-like features [7]. A specific pattern of low-grade DDLS, especially in the retroperitoneum, contains meningotheelial-

Fig. 2 Significant parts of the non-dedifferentiated component were almost completely myxoid (a). Some spindle cells in the fibro-myxoid areas showed focal nuclear enlargement and hyperchromasia corresponding to “atypical stromal cells” (b, arrows)

Fig. 3 The dedifferentiated, alipogenic component displayed significant variability in cellularity (**a**). The less cellular areas were composed of spindle cells with bland nuclear features and myxoid extracellular substance (**b**, **c**). The cellular areas were composed of

vaguely spindly to round cells with high nuclear to cytoplasmic ratio, overlapping, irregular and hyperchromatic nuclei. Note the mitotic figure just below the center (**d**)

Fig. 4 The immunohistochemical study showed that the well differentiated liposarcomatous component displayed strong expression of mdm2 (**a**, note the lipoblast—arrow) and cdk4 (**c**). Also the

dedifferentiated component was strongly positive for mdm2 (**b**) and cdk4 (**d**). Please note that the non-neoplastic components (lymphocytes and blood vessels present in **c** and **d**) show no protein expression

like whorls, i.e. concentrically arranged bland spindle-cells around small blood vessels [8, 9]. One such case has recently been described in the head and neck (retroesophageal) region [10]. Moreover, in one recently published case of DDLS with meningothelial whorls, the authors described an unusual vascular component with a Kaposi sarcoma-like histologic appearance [11]. The radiological diagnosis (both on computerized tomography (CT) and MRI) of DDLS may be fairly straightforward provided that the well differentiated component contains a significant proportion of fat. Radiographically, the CT features of lipomatous tumors are divided into 3 types (A–C) depending on the proportions and distribution of fatty and non-fatty components where DDLS falls under category C (=complex tumors with both a fat- and a well defined non-fatty component) [12]. A similar principle applies to MRI [13]. However, once a DDLS contains osseous or cartilaginous elements, the radiological diagnosis becomes challenging [14–16] and in the head and neck region the differential diagnosis of a teratoma becomes especially difficult. Moreover, (and as highlighted by our case) when a DDLS (or WDLS) contains abundant–predominant myxoid stroma (which is not an exceedingly rare event) [17], the radiological features may not point towards a neoplasm within the spectrum of adipocytic tumors.

The recognition that WDLS may display prominent myxoid features has led to the understanding that a significant number of (if not all) cases that previously were labeled as mixed well differentiated and myxoid liposarcomas, in fact represents heavily myxoid WDLSs [18, 19]. Moreover, awareness of this should help to avoid making an erroneous diagnosis of a myxoid liposarcoma and if in doubt perform immunohistochemical and/or molecular genetic studies for over expression/amplification of *mdm2*-*MDM2*/*cdk4*-*CDK4* and *CHOP*-*FUS* rearrangements, respectively.

DDLS has a marked tendency for local recurrence and distant metastasis and carry a sinister prognosis with a reported median survival of 5 months after the development of pulmonary metastases (from retroperitoneal DDLSs) [20]. The overall tumor-related mortality has been estimated to 30–50 %. DDLS of the head and neck region is unusual, accounting for only a few percent of DDLSs. This is highlighted by the fact that in many series of DDLS, only few cases have been located to the neck area; 1/155 cases [2], 0/30 cases [21], 0/16 cases [20], 0/75 cases [22], 1/12 cases [23], 0/24 cases [24], 1/32 cases [25] and from a 32 year experience of one institution of liposarcomas of the head and neck region, only 1 case of DDLS was identified [26].

The separation of DDLS into high- and low-grade variants is a contentious topic. Henricks and co-workers launched this idea in 1997 and based it on a set of morphological criteria, including low cellularity (approaching

that of a fibromatosis or low-grade fibrosarcoma), mild nuclear atypia and low mitotic activity (although a definitive cut-off for the latter was not specified) [2]. This concept has been challenged by Evans who requires a mitotic count of >5/10 high power fields (HPFs) in order to establish a diagnosis of DDLS [24]. Irrespective of the discussion on the validity of different grades within the spectrum of DDLS, it appears from the data that was presented by Henricks et al., that even low-grade variants are fully malignant tumors. In fact, 25 % (3/12) patients with pure, (25 % of 155 cases had co-existing low- and high-grade areas) low-grade DDLSs developed metastasis and 17 % (2/12) died of disease. None of the cases in the series by Henricks et al. had a dedifferentiated area with a size of <2 cm and site was the only factor that was prognostically significant on multivariate analysis (18 % of retroperitoneal tumors developed metastasis and 35 % died compared to only 15 and 11 %, respectively with tumors located to “accessible soft tissue” (of which 1 case was located in the neck). Also Japanese authors have presented data on the lack of prognostic relevance of low- versus high-grade DDLS [21], but again, none of these cases were located in the head and neck area. That liposarcomas of the head and neck region may carry a less sinister prognosis than in the retroperitoneum is suggested by a study by Fanburg-Smith et al. [27] who presented a series of 18 cases of LS (including well differentiated, myxoid and dedifferentiated subtypes) where no patients developed metastasis or died of disease.

DDLS is on a molecular genetic level characterized by amplified genes located to chromosome 12 (12q13-15) which consistently contain the *MDM2* gene and most commonly (90 % of cases) also the *CDK4* gene. These genetic aberrations are also present in well differentiated LS (WDLS) and thus constitute a strong argument for “true” biological progression of the “maternal” WDLS. Immunohistochemical detection of *mdm2* and *cdk4* and especially identification (on FISH) of amplification of *MDM2* (as in the case presented herein) and *CDK4* are most useful ancillary studies in establishing/suggesting a diagnosis of DDLS. This is especially valuable when confronted with limited biopsy-material where the alipogenic component is not represented (as in our case) or when dealing with a recurrence where the diagnosis is unclear and/or when the original tumor is not available for review. We retrospectively performed an immunohistochemical study on the limited biopsy material which was composed of cytologically bland cells and we detected strong nuclear and cytoplasmic expression of both *mdm2* and *cdk4*. Moreover, immunohistochemical detection of increased levels of p16 has also emerged as a diagnostically useful feature of both WDLS and DDLS [28, 29]. Also in our case did both the lipogenic and alipogenic

components display strong expression of p16. Similarly to mdm2 and cdk4, we performed retrospective immunohistochemistry for p16 on the limited biopsy material and the lesional spindle cells present were strongly positive.

Interestingly (but perhaps not surprising), is that the traditional definition of DDLS has been challenged in the sense that “genetically confirmed” cases of DDLS with high-grade features showing lipoblastic differentiation have been documented [20, 23, 30].

In conclusion, we have presented a case of dedifferentiated liposarcoma of the deep, cervical (paralaryngeal) soft tissue with a significant myxoid component, but otherwise characteristic histopathological, immunohistochemical and molecular genetic findings. Given the significant myxoid component, the tumor did not display characteristic radiological features for DDLS. The case presented initial diagnostic difficulties, mainly because of limited biopsy material from the sampled alipogenic, dedifferentiated, component which harboured significant heterogeneity with regards to cellularity, cytomorphology (nuclear atypia) and proliferative activity and where the lesional tissue in the biopsy was from a part of the tumor which showed deceptively bland morphological features. This report also emphasizes the value of applying immunohistochemistry for p16, mdm2 and cdk4 on sparse biopsy material from histologically low-grade spindle cell lesions in the head and neck region.

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