Clinical Oncology: Case Reports

Case Reports

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Primary Undifferentiated Neoplasm of the Left Arm with Characteristics of Extragonadal Germ Cell Tumor and High-Grade Sarcoma

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Abstract

A previously healthy man in his late 20s was diagnosed with a primary undifferentiated non-metastatic tumor of the left arm. After a biopsy, a clear pathological diagnosis could not be established. The tumor had positive immunohistological markers for both an extragonadal germ cell tumor and a high-grade sarcoma. Given the presumed germ cell etiology, he was started on empiric chemotherapy with etoposide and cisplatin. After a few cycles, the tumor showed dramatic response. However, due to poor patient follow-up, it progressed to massive size with severe compromise of the joint and critical neurovascular structures, which led to the decision for limb amputation. Post-surgical checkups showed no recurrence of the primary tumor or metastasis. This is the first report in the literature showing a tumor with these histological characteristics that responded to platinum-based therapy. It provides evidence for the need of more specific markers for the pathological evaluation of undifferentiated neoplasms.

Keywords: Extragonadal germ cell tumor; High-grade sarcoma; Undifferentiated neoplasm; Case report.

Introduction

Undifferentiated neoplasms are a heterogenous group of tumors missing a specific differentiation lineage or that have unidentifiable primary origin if based on morphological characteristics alone [1]. These entities are a diagnostic challenge, even with the increasing use of immunohistochemical and biochemical tumor markers. This obstacle is due in part to the large number of possible tumor origins and the lack of specific histological features [2]. Many of these tumors are eventually determined to be carcinomas or sarcomatoid carcinomas [1].

Studies have also demonstrated that given the tumor's morphology, location of the lesion, and patient's age, pathologists were able to correctly identify the neoplasm's tissue of origin in almost half the cases [3].

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Germ Cell Tumors (GCTs) may present as undifferentiated neoplasms, particularly extragonadal GCTs, representing between 1.6% to 5.5% of cases [2,4,5]. They are mainly found along the midline with the main sites being the anterior mediastinum, the retroperitoneal, hypophyseal and suprasellar regions, but rarely can appear outside midline structures [4-8].

Another important diagnostic possibility when evaluating undifferentiated neoplasms is soft-tissue sarcoma. In general, these tumors consist of a heterogeneous population of cells with mesenchymal features [9]. These cases present most commonly in the extremities of patients with a peak incidence from 60 years to 70 years of age [10,11]. Clinically they present as deep-seated, progressively enlarging masses with rapid growth that may be associated with local pain [12]. The main problem with the histological diagnostic approach of this tumor type is that cellular staining for markers such as vimentin, alpha-smooth muscle actin (α-SMA), CD34, and CD68 is neither sensitive nor specific [13].

Herein we introduce a case that presented a diagnostic and therapeutic dilemma: An undifferentiated neoplasm of the left arm that presented with multiple positive stains for highly sensitive and specific GCT markers without evidence of disease elsewhere in the body, and which partially responded to cisplatin-based chemotherapy.

Case Report

A male patient in his late 20s with no previous medical history presented to the orthopedics outpatient clinic. He came in with progressive enlargement of the proximal left arm, pain and limited range of motion characterized by the inability to abduct or forward flex his shoulder greater than 90° mainly due to the mass effect. He stated that the swelling worsened gradually throughout a month-long period, and only some days prior to the consultation did he start to experience pain. He denied paresthesia or weakness. He had a Magnetic Resonance Imaging (MRI) done because of a pain-related emergency visit prior to the consultation which showed a large heterogeneous soft tissue mass. Physical examination at that time confirmed the symptoms with the only additional finding being decreased sensation to light touch in the axillary nerve distribution.

An ultrasound-guided left shoulder mass biopsy was performed to establish the diagnosis, which showed a neoplasm with intact staining for INI-1 and SMARCA4. The tumor cells were also diffusely positive for OCT3/4, SALL4, AE1/3-CAM 5.2 (patchy) and MNF-116 (focal); negative stains included SMA, desmin, CD99, S100, CD45, AFP, hCG, PLAP, CD30, CDX-2, and glypican-3. Cytogenetics revealed negative FISH studies for isochromosome 12p. The pathological diagnosis was high grade malignant neoplasm after multiple revisions. However, given the cytokeratin positivity which suggested carcinoma and OCT3/4 and SALL4 positive staining a high suspicion for metastatic germ cell tumor was proposed, although a high-grade primitive sarcoma could not be ruled out.

The patient underwent multiple diagnostic studies without significant findings including a testicular US to rule out a primary site.. There was also no mediastinal or retroperitoneal involvement and both AFP and hCG were normal. A PET/CT showed an extreme-

-ly hypermetabolic heterogenous 11.6 cm x 7.0 cm x 8.0 cm mass in the left shoulder deltoid muscle and adjacent to the lateral aspect of the humeral head. Furthermore, extensive hypermetabolic regional axillary lymphadenopathy was present (Figure 1).

He was started on empiric chemotherapy with etoposide and cisplatin given the presumed germ cell etiology. Due to poor tolerability and follow-up, the patient only completed his first cycle in full. He received another 3 partial cycles and the tumor and axillar nodules responded partially to each incomplete treatment cycle. He then received additional palliative radiotherapy to the left shoulder but was not able to complete the full treatment course. His tumor was also submitted for somatic tumor profiling, which showed microsatellite status stable, a low tumoral mutational burden (4 Muts/Mb) and no reportable genomic alterations. He was lost to follow up for a brief period. Then five months after finishing radiotherapy treatment, he was seen again. At that time, tumor progression was seen on imaging with a mass that measured 14 cm x 2 cm x 12.2 cm x 17 cm and anterior humeral head dislocation. It was decided to start palliative gemcitabine but the patient missed several treatments. Furthermore, the tumor failed to respond and the mass expanded, significantly affecting the patient with pain and lack of function.

The patient was lost to follow up again for about six months. When he returned to care the patient reported that the mass continued to grow and became extremely painful. He also lost the use of his left arm and was unable to perform some daily functions. On MRI the tumor made up the entirety of his arm starting at the glenohumeral joint as shown in Figure 2. Ultimately, a consensus was made that the patient should undergo a left upper extremity forequarter amputation, axillary node resection and targeted muscle reinnervation at the left brachial plexus level. On pathology review of the resected specimen, the mass was still positive for SALL4 with

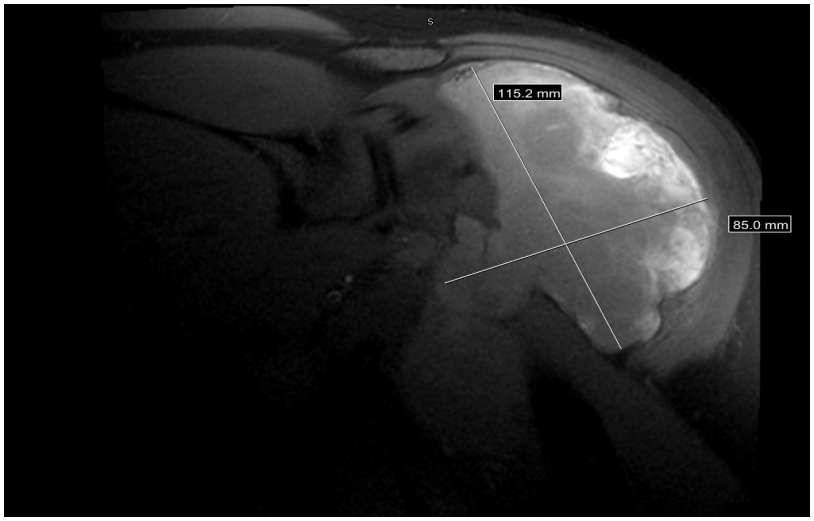

Figure 1: MRI of left arm showing large heterogenous soft tissue mass about the proximal humerus without evidence of bony involvement.

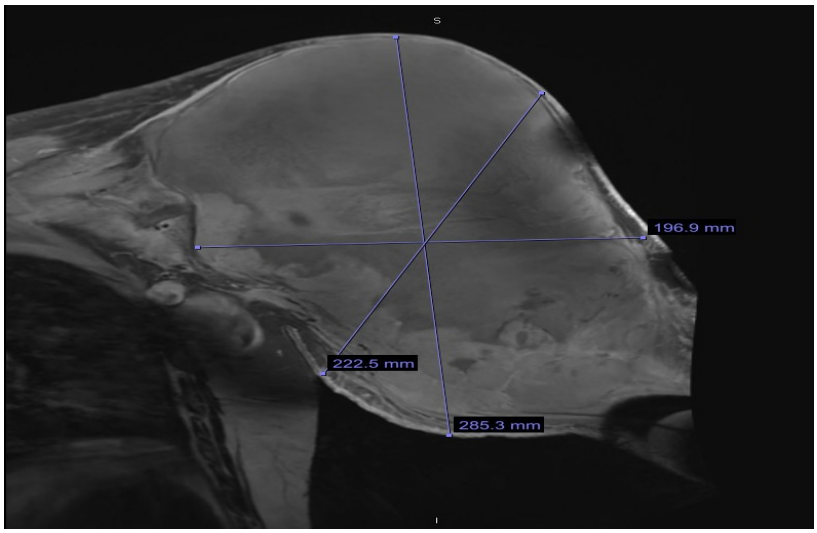

Figure 2: MRI showing massive left shoulder/upper arm mass with extensive osseous destruction of the humerus increased in size compared with the prior image with extensive likely metastatic left axillary lymphadenopathy.

morphological resemblance to the patient's prior biopsy. It was negative for AE1/3-CAM 5.2, CK20, CK7, WT1, ERG, CD68, chromogranin and synaptophysin. The axillary lymph node metastasis showed a poorly differentiated tumor consistent with germ cell neoplasm. Cells were positive for SALL4, OCT3/4 and focal AE1/3-CAM 5.2 and negative for PAX 5. The cellular component from both sites were identical. On further review, considering that the tumor had characteristics indicating that it could be a GCT, but the diagnosis of sarcoma could not be ruled out, a consensus was made that this was an undifferentiated tumor with primitive marker expression without a clear tissue of origin.

After the surgery, he was discharged without complications. However, he has continued to miss follow-up appointments and has only been seen in the immediate post-operative period at which time he reported continued mild pain without additional findings.

Discussion

Our case was diagnosed in the final histological report as an undifferentiated tumor with primitive expression markers. One of the primary methods used to establish germ cell origin of undifferentiated tumors is by identifying isochromosome 12p [2,14,15]. However, even though this is a highly useful diagnostic tool it is not present in all samples and its absence should not be a criteria to discard the possible diagnosis of a GCT [14]. On the other hand, it is important to point out that this tumor was positive for several immunohistochemical markers associated with germ cell tumors. OCT3/4 is considered an important regulator of the pluripotency capabilities and the self-renewal of normal embryonic stem and primordial germ cells (PGCs) [16]. The diagnostic utility of OCT3/4 has been explored in different reports as a marker for GCTs [17,18]. As it stands today, this marker is regarded as an absolute indicator of the presence of in situ/intratubular germ cell neoplasia [18]. The proliferation of the cells within the seminiferous tubules driven by specific Y chromosome encoded proteins coupled with the expression of KIT ligands in Sertoli cells drives them towards tumor genesis [15]. OCT3/4 promotes tumor formation by acting as an oncogene, with some studies even suggesting it as a potential therapeutic target [19]. Additionally, this patient's tumor had a positive stain for SALL4. This gene encodes proteins that regulate OCT4 working in the maintenance of pluripotency and self-renewal of embryonic stem cells [20]. Different studies have determined its utility as a stem cell marker for extragonadal germ cell tumors [21-23]. These reports have estimated high sensitivity compared to conventional and novel stem cell markers [21,22]. This includes PLAP, APF, and -CD30, all of which have limited sensitivity and or specificity when dealing with extragonadal GCTs [21]. This high sensitivity is also seen when compared to glypican-3, a novel maker previously used for diagnosing testicular yolk sac tumors (negative in this case) [24]. It has to be taken into consideration that these results reflect samples taken from mostly midline tumors, However, it has been suggested that due to their high sensitivity for germ cell tumors they should become part of the initial work up of undifferenced tumor at any location in patients of any age [1,22]. In addition, even though some studies have postulated that chemotherapy decreases the immunoreactivity of certain markers [25]; these GCT-sensitive markers are reportedly not affected by the use of previous chemotherapy [21,22]. This case would have probably benefited from the use of other highly sensitive GCT markers such as LIN28 or gene expression profiling by detection of either messenger RNA or microRNA as a way to further clarify its lineage [1].

There is still an ongoing discussion as to whether extragonadal GCTs are exclusively found in the midline. From our literature search a similar location for an extranodal GCT has only been reported once [6]. The main hypothesis regarding the formation of extragonadal GCTs states that PGCs originating from the proximal epiblast migrate along the midline of the body, then go through the hindgut to the genital ridge [26, 27]. This allows germ cell precursors to be misplaced through their trajectory. This theory is supported by the presence of extragonadal PGCs in the embryo [28]. PGCs are regarded as the main precursor to GCT due to their resemblance pertaining to their morphological and histological structure [26]. However, this theory would not explain this patient's tumor location. Another common line of thought is that extragonadal GCT represents a metastatic form of a primary gonadal GCT [29, 30]. This is based on evidence from some histological studies that found fibrous tissue and microlithiasis in the testicles of patients with concomitant GCT, regarded as evidence of a regressed primary lesion [26, 31]. A final theory is the "entrapment theory" postulated by Sano and colleagues [32]. It states that during the formation of the primitive streak PGCs might become entrapped in it or actively migrate with migrating mesodermal cells. Although this theory was first conceived to try to explain the generation of intracranial GCTs, we can see that many of the reported data in regards to extragonadal GCTs' topographic location have a common mesodermal origin [6, 7, 33, 34].

Finally, the initial therapy for this patient was chosen in accordance per NCCN guidelines for treating occult primary tumors in male patients younger than 40-years [35]. Their recommendation state that physician should be to treat the patient as a poor-risk germ cell tumor per their testicular cancer guidelines. Furthermore, previous reports have found that young patients with mediastinal and retroperitoneal undifferentiated neoplasms have responded to cisplatin-based combination chemotherapy in a way identical to what would be expected from tumors from germ cell origin [2]. As in the cited cases, this tumor also showed a high response to cisplatin-based chemotherapy. If we base in part our diagnosis on the tumor's therapeutic response, this could be considered an important clue in its assessment and diagnosis. It has been well-documented that testicular GCTs are susceptible to conventional cisplatin-based combination chemotherapy [36]. It has even led to an improvement in the overall survival of the disease with current 5-year relative survival reported as high as 95% [37]. Even though extragonadal GCTs are considered to have a worse prognosis, particularly nonseminomatous GCTs [38], current guidelines still recommend platinum-based combination chemotherapy due to its high level of response [39].

The main differential throughout the case was the possibility that the tumor represented a high-grade soft tissue sarcoma. The main point in favor of this diagnosis was the presence of positive cytokeratin markers. Undifferentiated pleomorphic sarcomas have been found to have aberrant expression of cytokeratin which tends to be focal [1]. Another important point is that even though most of the specific markers for this type of tumor came back negative, given the undifferentiated state of the pathological sample this could not be considered sufficient evidence to rule out the diagnosis [13]. Therapy guidelines for soft tissue sarcoma are oriented more towards surgical resection as a mainstay of therapy [13, 40]. The tumor in this case, fortunately, has not shown metastatic potential beyond locoregional lymph nodes and therefore, we believe he has been cured by resection.

Chemotherapy options for high-grade sarcomas are more geared towards metastatic disease, and first line anthracycline-based regimens are regarded as the main therapeutic approach [40]. The most commonly used drugs are ifosfamide and doxorubicin [41]. Another therapeutic option is the use of gemcitabine-based regimen [42]. However, Gronchi and colleagues determined in a recent clinical-trial that disease-free survival was superior in high-risk soft tissue sarcoma subjects receiving standard chemotherapy than those treated with a gemcitabine plus docetaxel regimen (HR 2.17, 95% CI, 0.98 - 4.80) [43], these findings which were later confirmed by a wider, open-label, multicenter randomized clinical trial [42]. Moreover, studies have found difficulties in the treatment of GCTs with sarcomatous components because the latter do not respond to the usual chemotherapeutic regimens [44]. As expected from a normal GCT, our patient responded partially to an incomplete therapy with etoposide and cisplatin which ultimately ended up regressing in part due to the lack of follow-up. He also showed some response with gemcitabine monotherapy which could be consistent with either proposed diagnosis.

Conclusion

Evaluation of undifferentiated neoplasms presents a diagnostic and therapeutic challenge. This case illustrates a tumor that expressed many highly sensitive markers for GCT despite the atypical location, and did show good to cisplatin-based empiric treatment. However, serological markers were normal and sarcoma remained in the differential, perhaps bolstered by the lack of metastatic behavior despite long periods without treatment. This case demonstrates the need for more specific markers for the pathological evaluation of undifferentiated neoplasms.

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