Trichilemmal carcinoma – a rare cutaneous malignancy: report of two cases

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Abstract
The trichilemmal carcinoma is a rare low-grade malignant lesion originating from hair follicle cells that usually occurs on sun-exposed skin of older individuals. A differential diagnostic is required with other skin carcinomas. We report two cases of trichilemmal carcinoma admitted at the Emergency University Hospital of Bucharest, Romania, in 2012, one of these cases being localized in the periorcular area and the other one resembling a cutaneous horn. These cases present several unusual aspects that are rarely described in the literature namely the site of the tumor which in the eyelid, development of a cutaneous horn, IHC tests which revealed EMA (epithelial membrane antigen) positivity in tumor cells. Considering that this type of tumor seldom develops metastases or local recurrences, and all the cases had free margins, there was no adjuvant therapy.

Keywords: trichilemmal carcinoma, adnexal tumor, sun-exposed skin neoplasm, immunohistochemical tests.

Introduction
Introduced by Headinton in 1976, the term “trichilemmal carcinoma” (TLC) has been adopted by pathologist after many years [1]. TLC is a malignant adnexal tumor with origin in the external hair sheath [2]. This rare tumor of the skin usually appears on the face, neck, the back of the hands, all these areas being sun-exposed. The incidence is high in elderly patients, the majority of the cases occurring in these areas being sun-exposed. The incidence is high in elderly patients, the majority of the cases occurring between the 7th and 9th decades of life [3]. The male to female ratio is sensible equal, without any gender predominance [4, 5].

The clinical appearance may be in the form of plaques, papules or nodules that may be ulcerated or present crusts [4]. This tumor present itself usually as a single lesion, but there have been reported cases presenting with multiple lesions [6]. It is frequently found within less than a year of evolution, presenting a fast growth [6].

In the majority of the cases, trichilemmal carcinoma is just locally invasive although the histological appearance is of a tumor with high-grade mitotic activity. Therefore, the clear margins obtained after surgical treatment demonstrates that adjuvant therapy is unnecessarily.

In the literature, the majority of authors sustained that there is no evidence of recurrence after complete excision [6–8], but seldom cases with recurrence or metastasis had been reported [9, 10].

The tumor shows a wide range of growth patterns (lobular, solid, trabecular). The tumor lobules are demarcated by a PAS+ hyaline membrane and contain large tumor cells with clear to eosinophilic cytoplasm, which reacts with PAS stain and does not stain for mucins. The pilar-type keratinization is also demonstrated by PAS stain reactivity. Some tumor islands show peripheral palisading. The lesion is mainly an intraepithelial tumor and it may associate an invasive component, which involves the epidermis up to the subcutaneous fat. In larger lesions, bleeding and/or necrosis were reported.

The diagnosis is established by histopathological examination on Hematoxylin–Eosin (HE) staining, completed when is necessary by immunohistochemistry. For TLC, immunohistochemical stains are usually negative for CEA (carcinoembryonic antigen) and EMA (epithelial membrane antigen) although positive results have been occasionally documented for the latter [7]. Cytokeratins expression of CK 1, 10, 14, 17 demonstrate that TLC’s origin is from follicular infudibulum [11].

A differential diagnosis is required; thus, squamous cell carcinoma, basal-cell carcinoma, keratoacanthoma and malignant nodular melanoma should be excluded.

The recommended treatment is Mohs’ technique or simple lesion excision [12].

Materials and Methods
We report two cases of trichilemmal carcinoma presented at the Emergency University Hospital of Bucharest, Romania, in 2012. Age, gender, localization of the tumor, macroscopic and microscopic description are noted for each one of the cases. After the surgical removal of the tumors, the tissue fragments were sent for processing and examination to our Department of Pathology. Tissue samples were fixed with 10% buffered formalin and sent for the histopathological processing.
by conventional method using inclusion in paraffin and HE staining. Also, immunohistochemical tests were performed. The paraffin blocks acquired by histopathological processing were section at microtome resulting sections with 3-μm thickness mounted on slides cover with poly-L-Lysine. After that, the sections were deparaffinized successively in baths of toluene and alcohol, one hour, 15 minutes by bath and rehydrated (three successive alcohol baths with decreased concentration: 96%, 80% and 70%, 10 minutes in each bath and followed by a bath with distilled water, where the sections were hold for 10 minutes). Washing in PBS (phosphate buffered saline), incubation with normal serum, for 20 minutes, incubation with primary antibody overnight, Dako LSAB kit, washing in carbonate buffer and development in 3,3’-diaminobenzidine hydrochloride/hydrogen peroxide and nuclear counterstain with Mayer’s Hematoxylin were made. We used the following antibodies from NeoMarkers LabVision: CEA, clone CEO5 (Thermo Fisher Scientific Inc., USA, 1:200 dilution), High Molecular Weight Cytokeratin, clone 34βE12 (Thermo Fisher Scientific Inc., USA, 1:50 dilution), CK34βE12 (dilution 1:50), Epithelial Membrane Antigen (EMA), clone E29 (Thermo Fisher Scientific Inc., USA, 1:50 dilution) and S-100 protein, clone 4C4.9 (Thermo Fisher Scientific Inc., USA, 1:100 dilution). The immunoreactive cells from each case were evaluated as follow: diffuse positive, >75% positive cells; positive, 25–75% positive cells; focal positive, <25% positive cells and negative cells. Our findings will be compared with the literature.

**Results**

**Case No. 1**

An 84-year-old female patient presented to our hospital in June 2012 with injuries after falling down. In this circumstance, the bleeding tumor involving the periocular area was identified. The patient was referred to the Department of Plastic Surgery where, after a slit-lamp examination, the excision of the lesion was performed. The excised skin fragment sent to the Department of Pathology measured 20/18/7 mm after being kept in formalin. The excision piece presented a grey, irregular, exophytic tumor of 10/12/7 mm, with increased consistency and areas of ulcerations and bleeding. The histopathological examination showed an actinic damaged skin with multiple different sized cells forming slightly demarcated lobules. The cells presented moderate pleomorphism, hyperchromatic nuclei, clear or slightly eosinophilic, PAS+ cytoplasm, as well as atypical mitotic figures. Also, trabecular pattern or lobules with peripheral palisading, pushing margins and infiltrative growth can be seen (Figures 1–3). The surrounding stroma was desmoplastic, representing a clear response to the infiltrative tendency of the tumoral islets. Inflammatory cells were seen rarely in the tumoral stroma. The tissue margins were clear of tumor cells. Immunohistochemical tests were performed in order to clarify the origin of the tumoral cells. Focally positive high molecular weight cytokeratin CK34βE12 (Figure 4) as well as diffuse positive EMA (Figure 5) demonstrates the epithelial origin, whereas the negativity of CEA (Figure 6) and S-100 protein distinguishes it from different adenocarcinomas or melanoma. The diagnosis was ulcerated trichilemmal carcinoma and the tumor was excised with free-tumor margins.

**Case No. 2**

A 90-year-old female presented to the hospital in July 2012 with a lesion on the frontal region clinically diagnosed as a cutaneous horn. The lesion was treated with a simple excision. The tumor was whitish, measured 21/18/47 mm, and had an exophytic growth with mild increased consistency and irregular surface.

Histopathologically, the tumor was composed of epithelial lobules admixed with a trabecular and rare solid infiltrative pattern of growth. The cells had clear cytoplasm and hyperchromatic nuclei with frequent atypical mitotic figures. The desmoplastic stroma presented focal fibrosis and rare inflammatory cells. Immunohistochemistry was carried out and showed similar changes as described in the previous case, with lobules of clear cells originating from the hair follicle. In that matter, CK34βE12 was positive whereas S-100 protein and CEA were negative. EMA was also performed, showing a diffuse positivity and therefore demonstrating once again the epithelial origin of the tumor. Finally, the diagnostic was ulcerated trichilemmal carcinoma. The tumor was completely excised and revealed free of tumor safety margin on conventional histopathological examination.

![Figure 1 – Trichilemmal carcinoma: actinic damaged skin. HE staining, 40×.](image1)

![Figure 2 – Trichilemmal carcinoma; infiltrative growth pattern of tumoral lobules with a sharply defined border and pushing margins. HE staining, 40×.](image2)
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Figure 3 – Trichilemmal carcinoma: variable nuclear pleomorphism with mitotic activity. HE staining, 200×.

Figure 4 – Trichilemmal carcinoma: CK34βE12 focal positive, 100×.

Figure 5 – Trichilemmal carcinoma: EMA diffuse positive, 100×.

Figure 6 – Trichilemmal carcinoma: CEA negative in tumoral cells, 100×.

Discussion

Benign and malignant tumors of skin appendages are of wide spectrum. They can originate from one or more types of adnexal structures found in histological normal skin [13].

TLC is an adnexal tumor derived from the outer layer of the hair follicle of the skin. It has a low incidence and it is found primarily on elderly people’s skin due to solar radiations exposure [9]. The most frequent sites for this type of tumor are the head, neck and back of hands but other areas like left suprACLAVICULAR region [4], tight [10], anterior thoracic wall [12], upper lip [14] or eyelid [15, 16] were reported. Moreover, a case of axillary TLC with aggressive growth was reported, leading to the amputation of the upper limb, partial resection of the thoracic wall followed by reconstruction [17].

Regarding our patients, one tumor was on the forehead, a common region for TLC, whereas the other involved the eyelid. This latter location is very rare but it is a hair-bearing, sun-exposed area as well. Our two patients had a mean age of 87 years, which concords with the fact that this tumor affects most frequently the elderly. Rare cases of TLC occurring in young patients: 35-year-old male [12], 25-year-old male [15], as well as a case with multiple tumor presentation of TLC [6] were also reported in the literature.

The pathogenesis for this carcinoma is not clear, but sun-exposure [18], post-surgical radiation for other lesions (basal cell carcinoma for example) [12], immunosuppression after renal transplantation [19] or a pre-existing burn scar [20] predispose to the development of TLC (although this issue is still under investigation). Long exposure to radiations, for example, more than 50–60 diagnostic chest radiographs, is also a presumably risk factor [21, 22]. There was described a case of trichilemmal carcinoma in association with xeroderma pigmentosa [14]. Also, arsenic intake or bullous pemphigoid history were reported in various cases [23]. Chronic mechanical stimulation, as well as malignant transformation of a trichilemmoma could be incriminated [23]. In our case report, both lesions were in sun-exposed but repetitive traumatized areas. No history of burns, arsenic exposure, immunosuppressive medication or other above-mentioned pathology is known.

Both our patients were women, demonstrating once again the higher incidence among elder women. The cause for this higher incidence is not clear, but hormonal changes of menopause can be, at least in some cases, a subsidiary pathogenic factor for TLC and other skin carcinomas [24].

Clinically, the tumor may appear as a white or pale tan papule, as a plaque or nodule, presenting ulceration, hyperkeratosis or scabs [6], usually having less than 3 cm
in the greater diameter. It is a solitary lesion, in general measuring 3 cm in its greater diameter [2], although multiple presentations have been reported [21, 24]. These tumors can also be associated with multiple trichilemmoma within Cowden’s syndrome [13]. The tumors in our cases had a mean greater diameter of 1 cm, one was ulcerated and easily confused with a cutaneous horn. As noted by Wang et al., such tumors presenting with excessive keratinization can be clinically misdiagnosed as cutaneous horns [23].

Microscopically, in TLC proliferating clear cells in lobular or trabecular pattern originating from pilosebaceous structures can be observed. The clear cell aspect is due to the glycogen-rich cytoplasm making the tumor difficult to distinguish from clear cell variants of BCC or SCC. The accumulation of glycogen in the cytoplasm makes it positive in PAS staining. In the large majority of the cases, the lobules are infiltrative, with peripheral palisading consisting of with high-grade atypical cells with frequent abnormal mitotic figures. Thick basement membrane [21] as well as pagetoid spread can be observed [4]. Foci of trichilemmal keratinization, horn cyst, intratumoral hemorrhage and necrosis or cells with subnuclear basal vacuolization can also be seen [23]. No specific stromal aspects are described in the literature. The large majority of the microscopic aspects were detected in our cases. However, immunohistochemical tests were performed in order to certify the diagnosis. Normally, TLC is positive for cytokeratins, namely CK 1, 10, 14, 17 and 19 [11] and sometimes for EMA, attesting the hair origin, and negative for CEA, S-100 protein and other cytokeratins (CK 7, 8, 15, 16, 18 and 19) [26]. The last three stains are used to differentiate TLC from other tumors such as clear cell eccrine carcinomas or visceral clear cell adenosarcomas as well as melanomas. Our cases met all the immunohistochemical criteria.

The differential diagnostic for trichilemmal carcinoma includes other skin cancers, especially those with clear cells. It is easy to confuse TLC with basal cell carcinoma (BCC) [6, 8], but the clear cell aspect associated with subnuclear vacuolization or trichilemmal keratinization assesses the TLC diagnosis. Squamous cell carcinoma that demonstrates cellular atypia and clear cytoplasm is similar to TLC. The difference is that SCC lacks pilar differentiation, trichilemmal keratinization or lobular proliferation pattern as well as peripheral palisading and vacuolization [7, 8]. The main difference between sebaceous carcinomas and TLC is that in sebaceous tumoral lobules presents with PAS negative, eosinophilic cells at the periphery [8, 27]. TLC differs from malignant proliferating trichilemmal tumors, the latter presenting a lobular proliferation around the pilosebaceous unit, always with connection to the epidermis [28]. Also, differential diagnosis must be made with cutaneous metastases of renal clear cell carcinoma or other low-differentiated carcinoma [23]. TLC is often confused with many other pathologies like keratoacantoma, Bowen’s disease, Paget’s disease, mucin-producing carcinomas or balloon cell malignant carcinomas [17].

It is imperative that the correct diagnosis is made as TLC, despite the cytological malignant appearance, has an indolent course and exceptionally can metastasize [14].

The recommended treatment for trichilemmal carcinoma is surgery. Histological clear margins must be documented because of the potential recurrence and the potential local aggressive course. In a study conducted by Zhuang et al., from a total of 26 patients, only two patient presented recurrence after a wide local excision with tumor-free margins [22].

Cutaneous tumors have been reported previously to have spontaneous regression. Regarding trichilemmal carcinoma, only one case of spontaneous regression was documented [29].

Since this neoplasm has a benign clinical course and it can easily be treated with free-tumor margins excision, there is no suggestion of alternative or adjunctive therapy need [30]. If any metastasis occurs, chemotherapy is needed, still, there is not a clear consensus regarding the substances or the doses that should be used [31].

Conclusions

Although trichilemmal carcinoma is a rare skin appendage tumor, the clinician and the pathologist have to consider it in the differential diagnosis of a lesion on the hairy sun-exposed skin, especially if the patient is elderly. Consequently, an indurated skin nodule or an ulcerated mass even on the eyelid – an extremely rare site for this tumor – can raise the suspicion of TLC. Still, trichilemmal carcinoma should be accounted after more frequent pathologies have been excluded. Many questions regarding this tumor are still unanswered. What are the main triggers? What is the explanation of the good prognosis especially in the light of high-grade malignant appearance? Nonetheless, TLC remains a challenge for the pathologist and further investigations are necessary in order to fully understand this pathology. Generally, this slowly growing tumor has a benign clinical evolution, but its potential for local invasion and recurrence raises the necessity for tumor free margins and careful follow-up to all patients.

References

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