Keratoacanthoma centrifugum marginatum: an unusual clinical and histopathological diagnostic pitfall

TIBERIU-AUGUSTIN GEORGESCU1,2), ANA MARIA OPROIU2,3), MIHAI GEORGE RĂDĂŞAN3), ADRIAN VASILE DUMITRU1,2), DIANA COSTACHE2), OANA MARIA PĂTRAŞCU1,2), ANCA MIHAELA LĂZĂROIU1), ALINA ELENA CHEFAN4), MARIA SAJIN1,2), MARIANA COSTACHE1,2)

1)Department of Pathology, University Emergency Hospital, Bucharest, Romania
2)"Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
3)Department of Plastic Surgery, University Emergency Hospital, Bucharest, Romania
4)Department of Pathology, Dorset County Hospital, Dorchester, United Kingdom

Abstract
Keratoacanthoma centrifugum marginatum (KCM) is a very rare variant of keratoacanthoma characterized by progressive peripheral growth accompanied by central healing. The tumor has the peculiar ability to involute spontaneously. A careful differential diagnostic with other skin carcinomas or hyperkeratotic lesions is required in order to ensure appropriate clinical management. We report a case of KCM in a 62-year-old man presenting with a solitary, large exophytic, sessile tumor located on the ventral side of the right lower leg, which developed over the course of one year from an initial erythematous papule. The patient presented history of local trauma. To our knowledge, this is the second report in the scientific literature supporting a possible traumatic etiology. Due to its rarity and lack of distinctive histopathological features, KCM poses a difficult diagnostic challenge. Therefore, the importance of an accurate histopathological examination and extensive use of ancillary studies for differential diagnosis is emphasized.

Keywords: keratoacanthoma, keratoacanthoma centrifugum marginatum, immunohistochemistry.

Introduction
Keratoacanthoma (KA), also known as molluscum sebaceum, is a rapidly growing and locally destructive tumor, which appears on hair-bearing skin, at sites of minor injury or sun damage. Although, strictly speaking, KA is not a tumor of the epidermis, it features many histopathological similarities to squamous cell carcinoma (SCC). In fact, some authors classify it as a variant of regressive squamous cell carcinoma [1, 2], while others prefer to make a strict differentiation between these two entities based on gene expression [3] and/or expression of cutaneous markers [4].

Either way, it is now commonly accepted that unlike squamous cell carcinoma, keratoacanthoma does not develop from normal epidermal keratinocytes and is composed of keratinizing squamous cells derived from the supraseboglandular parts of hair follicles. It manifests as a firm, rounded, flesh-colored or reddish papule, which usually resolves spontaneously, even when left untreated [5–10].

Incidence of keratoacanthoma appears to be higher in white-skinned middle-aged to elderly patients and somewhat lower in Asians and dark-skinned individuals. Scientific studies reveal that KA tends to be up to three times more often in males than in females and extremely rare in children.

Keratoacanthoma centrifugum marginatum (KCM) is an extremely rare variant of keratoacanthoma first described by Miedzinski & Kozakiewicz, in 1962 [11], and classified as a different entity by Belisario, in 1965 [12]. Although locally destructive, it is generally accepted that KCM is a benign entity, as, to our knowledge, no metastatic cases have been reported yet [13]. Moreover, the development of multiple KAs and KCM in the same patient is extremely rare and has been previously reported in only three cases [14].

The aim of this paper was to emphasize the impact of proper immunohistochemical analysis in establishing the correct diagnosis of KCM and to highlight the importance of careful histopathological examination, when dealing with such rare cases.

Case presentation
We report the case of C.G., a 62-year-old man presenting to the Department of Plastic Surgery of the University Emergency Hospital Bucharest, Romania, in early November 2016 (10.11.2016), with recommendation for surgical excision of a single large exophytic, sessile tumor located on the ventral side of the right lower leg, which developed over the course of one year from an initial erythematous papule. The patient had no history of any type of keratoacanthoma or any personal or familial history of malignancy. There was no documented interaction or use of immunosuppressive drugs and/or other chemicals including alcohol or smoking. However, he reported being involved in a bike accident in 2003, which resulted, among other bruises, in a slowly healing traumatic wound on the ventral side of the lower leg. Routine laboratory tests were normal and serology for human immunodeficiency virus was negative. Physical inspection revealed no internal organ malignancy. Complete surgical excision with grafting was successfully performed and the specimen was sent to the Department of Pathology in
the same Hospital Unit for histopathological assessment.

Gross examination revealed a single, irregular, 157×
115×15 mm greenish-white crater-like lesion with hyper-
keratotic, bluish and brown margins, which exhibited a
tendency to expand peripherally to the ventral side of the
right lower leg. The lesion appeared firm, non-tender, non-
indurated and not attached to the underlying structures
(Figure 1).

Figure 1 – Gross aspect of the single, irregular, 157×
115×15 mm greenish-white crater-like lesion with
hyperkeratotic, bluish and brown margins.

Tissue samples were fixed with 10% buffered formalin
and were processed by conventional histopathological
method, using inclusion in paraffin and Hematoxylin–
Eosin (HE) staining. Also, immunohistochemical (IHC)
tests were performed, using the following antibodies: pan-
cytokeratin (CK), clone AE1/AE3 (Thermo Fisher Scientific
Inc., USA, 1:100 dilution); CK 19, clone D5/16 B4 (Thermo
Fisher Scientific Inc., USA, 1:50 dilution); p53 protein,
clone DO-7 (Thermo Fisher Scientific Inc., USA, 1:100
dilution); Ki-67, clone SP6 (Thermo Fisher Scientific Inc.,
USA, 1:200 dilution); bcl-2, clone 8C8 (Thermo Fisher
Scientific Inc., USA, 1:100 dilution); p16, clone G 175-
405 (Thermo Fisher Scientific Inc., USA, 1:200 dilution);
proliferating cell nuclear antigen (PCNA), clone PC10
(Thermo Fisher Scientific Inc., USA, 1:200 dilution). IHC
results were evaluated as follows: diffuse positivity in
more than 75% cells was labeled as “positive”, areas with
25–75% positive cells were labeled “focal positive”, and
weak positivity in less than 25% cells was considered
“negative”.

Histopathological (HP) examination revealed a large
squamoid-type proliferative lesion with keratin-filled
craters and several horn cysts. The adjacent epidermis
exhibited pseudoepitheliomatous hyperplasia extending
over the sides of the crater (Figure 2), while the underlying
dermis revealed marked solar elastosis. Tumor cells were
bland, well differentiated, with pale eosinophilic and
glassy cytoplasm, featuring a striking tendency towards
keratinization. Mitoses were mostly inconspicuous,
invariably normal and present predominantly within the
proliferative epithelium, at the periphery of the tumor
lobules. Although tumor growth followed a downward
direction, it did not extend beyond the depth of the sweat
glands glomeruli (Figure 3). The lesion had a well-
demarcated regular base, accompanied by scant lympho-
plasmocytic infiltrate and variable numbers of neutrophils,
eserinphils and histiocytes. This tumor is quite large and
relatively deeply infiltrative, and the term “keratoacan-
thoma-like squamous cell carcinoma” might reasonably be
applied to it. However, there is more keratinization than is
usual in squamous cell carcinoma, giving the tumor islands
a glassy appearance (Figure 4). The lesion lies above the
level of the sweat glands coils in the dermis. Tissue cultures
and stainings did not reveal any infectious organisms.

Keratoacanthoma frequently mimics squamous cell
carcinoma, both clinically and histopathologically. Immuno-
staining for CK 19, CK AE1/AE3, p16, p53, Ki-67, PCNA
and bcl-2 has been conducted in order to make a clear
distinction between these two potential diagnoses with
extremely different clinical outcomes and results were
rather conclusive. CK AE1/AE3 showed prominent cyto-
plasmic and membranous staining of the neoplastic cells
(Figure 5), while CK 19 immunostaining revealed sweat
duct entrapping within the neoplastic tissue (Figure 6).
Ki-67 proliferation index was very low, with positive nuclear
staining observed almost exclusively in the basal and supra-
basal keratinocytes (Figure 7). PCNA followed a similar
pattern in terms of both intensity and percent of stained
cells. P53 immunostaining revealed positive nuclear staining
along the outermost layers of the aggregates of neoplastic
cells (Figure 8). The uniform loss of bcl-2 in all areas
(Figure 9) and negative p16 immunostaining (Figure 10)
contributed to the final diagnosis of keratoacanthoma.

Figure 2 – Keratoacanthoma: the epidermis, partially
necrotic, extends like a buttress over the side of the
central crater; irregular epidermal proliferations extend
downward into the dermis (HE staining, ×40).

Figure 3 – Keratoacanthoma: the lower area of KCM,
revealing a well-demarcated, regular base, which does
not extend beyond the depth of the sweat glands,
accompanied by scant lympho-plasmocytic infiltrate (HE
staining, ×40).
Figure 4 – Keratoacanthoma: the upper area revealing a squamoid proliferative lesion with several keratin-filled horn cysts lined by bland, well-differentiated tumor cells with pale eosinophilic and glassy cytoplasm (HE staining, ×100).

Figure 5 – Diffuse appearance of positive pan-CK AE1/AE3 in the tumoral cells [IHC staining with 3,3’-diaminobenzidine (DAB) chromogen, ×100].

Figure 6 – Microscopic appearance of CK 19 positivity revealing eccrine gland entrapping within the neoplastic growth (IHC staining with DAB chromogen, ×200).

Figure 7 – Microscopic appearance of Ki-67 proliferation index, which was very low, with positive nuclear staining observed almost exclusively in the basal keratinocytes (IHC staining with DAB chromogen, ×100).

Figure 8 – Microscopic appearance of p53 nuclear immunostaining along the outermost layers of the aggregates of neoplastic cells (IHC staining with DAB chromogen, ×100).

Figure 9 – Bcl-2 negative in tumoral cells (IHC staining with DAB chromogen, ×200).
Based on all these clinical, HP and IHC findings, the final diagnosis of keratoacanthoma centrifugum marginatum was established.

Discussion

Keratoacanthomas are usually solitary but can also be multiple [10]. There are three clinical subtypes of solitary keratoacanthoma: giant keratoacanthoma, keratoacanthoma centrifugum marginatum and subungual keratoacanthoma. Multiple keratoacanthomas are also classified into several subtypes, such as: Ferguson–Smith type KAs, Grzybowski type KAs, Witten & Zak type and Muir–Torre syndrome [15–19].

Multiple Ferguson–Smith keratoacanthoma is a rare autosomal dominant disorder characterized by self-healing keratoacanthomas arising in early adulthood. Eruptive keratoacanthoma of Grzybowski is usually defined by a generalized eruption of several dome-shaped, skin-colored papules of 2–7 mm diameter, which do not appear on the palms and soles. Keratoacanthoma may be a constituent of Muir–Torre syndrome, which is a cancer-associated genodermatosis involving several sebaceous neoplasms (adenomas, epителиomas, and carcinomas), keratoacanthomas, and gastrointestinal malignancies (usually of the colon). Genito-urinary, pulmonary and endometrial carcinomas have also been reported in association with Muir–Torre syndrome. When Muir–Torre syndrome is suspected, an age-appropriate cancer screening workup is recommended.

KCM (multinodular keratoacanthoma) appears to be an acquired disorder of adulthood, usually affecting white males in the 5th decade of life [8], being somewhat less frequent in Asians and dark-skinned individuals. The exact pathogenesis of KCM has not been established yet. Heredity, viruses, smoking, chronic ultraviolet light exposure and various chemical carcinogens such as insecticides, printing chemicals, mineral oil, tar or pitch have been suspected by multiple authors to be involved in the etiology of all forms of KAs, including KCM. Genetic mutation of transforming growth factor beta-1 (TGF-β1) might play a crucial role in the pathogenesis of this tumor as proposed in the study of Ferguson–Smith and acknowledged by Goudie et al. [20].

Clinically, KCM features progressive peripheral expansion reaching up to 20 cm, with elevated, rolled-out margins and central healing followed by atrophy [8, 9, 21, 22]. It can appear anywhere on the body, being more frequent on chronic sun-exposed areas like dorsum of the hands and legs [23]. However, unlike traditional KAs, which have been reported to appear after trauma, KCM is rarely related to a traumatic event [13, 14] and does not show tendency for spontaneous regression. Dominiak et al. [24] recently reported a case of trauma-associated KCM, which, to our knowledge, is the first case of this type described in the scientific literature. Our case also presented history of local trauma, therefore being the second report in the scientific literature supporting this possible etiology.

The tumor often presents as a solitary lesion affecting mainly adults, but there have been recent reports of these peculiar tumor-affecting patients in early childhood. Multiple tumors have also been reported. Moreover, all cases have been reported in adult males.

KCM is often confused with SCC both clinically and histopathologically. KAs tend to grow rapidly, then involute, unlike well-differentiated invasive squamous cell carcinomas, which grow relatively slow and never involute. Rapid growth after a biopsy is usually suggestive for the diagnosis of KA. Perineural and perianexial extension may be seen in both entities, but KCM rarely extends, if ever, beyond the depth of the sweat glands. In contrast, the presence of acantholysis favors the diagnosis of SCC. Neutrophilic microabscesses, eosinophilic infiltrates, iron deposition and elastic trapping are common in KA, but rarely seen in SCC. Pseudopitheliotomatous (pseudocarcinomatous) hyperplasia (also known as Borst–Jadassohn phenomenon) and hypergranulosis of the hair follicles occur in the central portion of early KAs but only at the periphery of SCCs. Another major feature of a KA is its capacity to undergo terminal differentiation, a process by which the tumor will eventually disappear.

Another main differential diagnosis of KCM involves giant KA, which can be distinguished from KCM by the absence of underlying tissue destruction and downward vertical spread.

KCM can also mimic a regressing KA. The former has massive keratin within the crater, out of proportion to the thin epithelium that lines the scalloped crater.

Other differential diagnoses include: verrucous carcinoma, lupus vulgaris, botryomyosisis, blastomycosis-like pyoderma and pseudopitheliotomatous hyperplasia, hypertrophic lupus erythematosus, atypical mycobacterial infections, or deep fungal infections [25]. With such an extensive differential diagnostic list, a lesion generally too large to be treated by classic excisional biopsy, and with histological features that overlap with those of many other similar lesions, KCM requires an extra careful approach from both the clinician’s and pathologist’s point of view.

Surgical excision is the preferred therapy for solitary KA as well as for KCM. However, the latter being larger, involves a much wider excision and this is not always achieved upon first surgical intervention, rising questions about the most convenient therapy for each particular case. There are reports of KCM successfully treated with oral retinoids [9] and also with topical 5-fluorouracil, intralesional injection of methotrexate, interferon alpha, or bleomycin. However, no official protocol has been
established for this kind of lesions. Our patient was treated only by complete surgical excision and following discharge from hospital, there were no additional events observed at the regular follow-ups.

Conclusions

Only through an elaborate intertwining of clinical history and immunohistopathological features, one may establish the appropriate setting for accurately diagnosing KCM and predicting therapeutic outcome. When there is any doubt about the potential biological behavior of a suspicious lesion that resembles KA, complete surgical excision, as for squamous cell carcinoma, is recommended. After resection, immunohistochemical assessment of p16, p53 and Ki-67 proliferation index can be extremely useful in establishing a differential diagnosis between well differentiated SCC and KA. Due to the rarity of this lesion in Romania and worldwide, few clinical, pathological, therapeutic and prognostic features of this particular tumor have been discussed in previous scientific studies. We highlight the possibility of trauma being an etiological factor for KCM and the crucial importance of immunohistochemistry for establishing the correct final diagnosis.

Conflict of interests

The authors declare that they have no conflict of interests.

Ethical standards

We undersign, certificate that the procedures and the experiments we have done respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000, as well as the national law.

References


Corresponding authors

Adrian Vasile Dumitru, MD, PhD Student, Department of Pathology, University Emergency Hospital, 169 Independenţei Avenue, 050098 Bucharest, Romania; Phone +40727–596 905, e-mail: dr.adriandumitru@yahoo.com

Ana Maria Oproiu, Lecturer, MD, PhD, Department of Plastic Surgery, University Emergency Hospital, 169 Independenţei Avenue, 050098 Bucharest, Romania; Phone +40720–070 359, e-mail: anamariaoproiu@gmail.com

Received: June 21, 2016     Accepted: July 7, 2017