MAMMAGLOBIN IMMUNOSTAINING IN THE DIFFERENTIAL DIAGNOSIS BETWEEN CUTANEOUS APOCRINE CARCINOMA AND CUTANEOUS METASTASIS FROM BREAST CARCINOMA

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Summary

The differential diagnosis between cutaneous apocrine carcinoma (CAC) and cutaneous metastases from breast carcinoma is commonly difficult. Many times, clinical information is crucial in the final diagnosis, because help that can be obtained from immunohistochemistry is usually limited concerning this subject.
We used the antibody mammaglobin in order to study 10 cases of cutaneous metastasis of ductal breast carcinoma, and 2 cases of CAC. One of the CAC cases showed only scattered positive cells, while the other did not show any positivity. Four cases of metastatic breast carcinoma also showed scattered positive cells. In other five metastatic cases, positive cells were abundant, representing up to 60% of the tumoral cells. One case of metastatic breast carcinoma did not show any expression of mammaglobin at all. Although, more cases of CAC should probably be studied in the future before any categorical conclusion can be obtained, our results seem to indicate that a pattern of immunostaining with expression of mammaglobin in many cells would favor a metastatic origin of the tumor.

Key words: mammaglobin – apocrine gland carcinoma – metastatic carcinoma – ductal carcinoma – breast

Souhrn

Imunohistologický průkaz mamaglobinu v diferenciální diagnostice mezi apokrinním karcinomem kůže a kožní metastázou karcinomu prsu

Diferenciální diagnóza mezi apokrinním karcinomem kůže (AKK) a kožní metastázou karcinomu prsu je často obtížná. Spíše než imunohistologie může pomoci klinická informace.
Použili jsme protilátku mamaglobin k vyšetření 10 případů kožní metastázy duktálního karcinomu prsu a 2 případů AKK. V jednom z případů AKK byly pozitivní jen ojedinělé buňky, druhý případ byl negativní. Z 10 případů metastázy karcinomu prsu byly v 5 pozitivní buňky četné (až 60 % nádorových buněk), ve 4 byly pozitivní ojedinělé buňky a 1 případ byl negativní.
Jsme si vědomi, že by bylo v budoucnu vhodné vyšetřit více případů AKK než bude možno vyslovit kategorický závěr; naše výsledky však ukazují, že imunohistologický průkaz exprese mamaglobinu v četných buňkách nádoru může svědčit pro jeho metastatický původ.

Klíčová slova: mamaglobin – karcinom apokrinní žlázky – metastatický karcinom – duktální karcinom – prs

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Cutaneous apocrine carcinoma (CAC) is an elusive malignancy among the adnexal tumors. On the contrary to other adnexal tumors, the differential diagnosis with a cutaneous metastasis from a breast carcinoma is extremely difficult, up to the point that many reports emphasize how crucial the clinical information is. The immunohistochemistry has not been of much help in order to discriminate between both conditions. Many of these thoughts are presented in a recent article by Adámková et al. (3).

Mammaglobin is a relatively new antibody that intensively stains ductal breast carcinomas. Although the staining pattern with mammaglobin has been investigated in certain benign apocrine tumors, its expression has not been checked in CAC.

In this report, we investigated the expression of mammaglobin by two CACs, as well as by 10 cutaneous metastases from ductal breast carcinoma, in order to check if mammaglobin might help in the differential diagnosis between them.

MATERIAL AND METHODS

The cases were recovered from our archives, revising the hematoxylin-eosin slides.

We performed an immunohistochemical study in all the cases, with the monoclonal mouse anti-human mammaglobin antibody of DakoCytomation (Clone 304-1A5; code N1637), and with the Dako REAL EnVision detection system.

RESULTS

The details about the selected cases, including location of the tumors and gender and age of the patients are shown in table 1.

One of the CACs showed a common tubular morphology (Fig.1; bottom), while the second had a cribriform pattern (Fig. 1; top). This latter case has been reported on its own before (13).

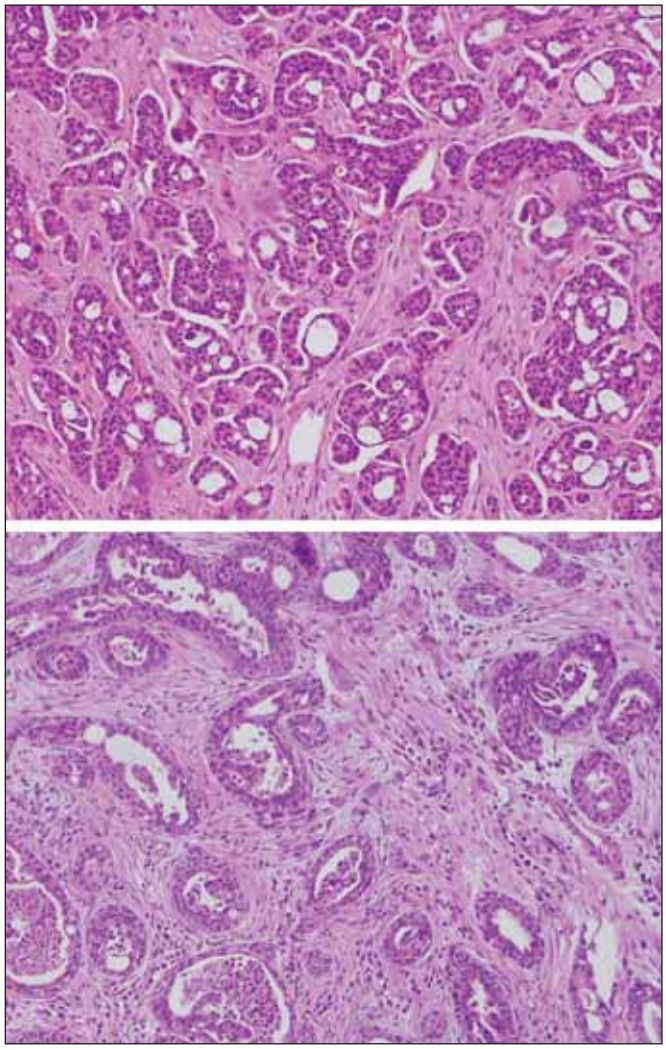

Fig. 1. The two cases of CAC showed a cribriform (top) and tubuliform (bottom) pattern, respectively.

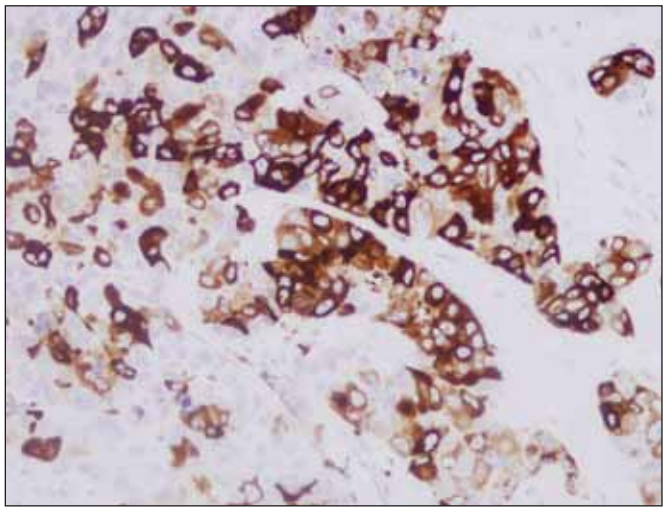

Fig. 3. Abundant positive cells expressing mammaglobin were observed in five of the metastatic cases.

In the immunohistochemical study, one of the cases of CAC (case number 2) showed only scattered positive cells (Fig.2.A), while the other did not show any positivity. Four cases of metastatic breast carcinoma showed a similar pattern of immunostain like the one observed in case number 2, with

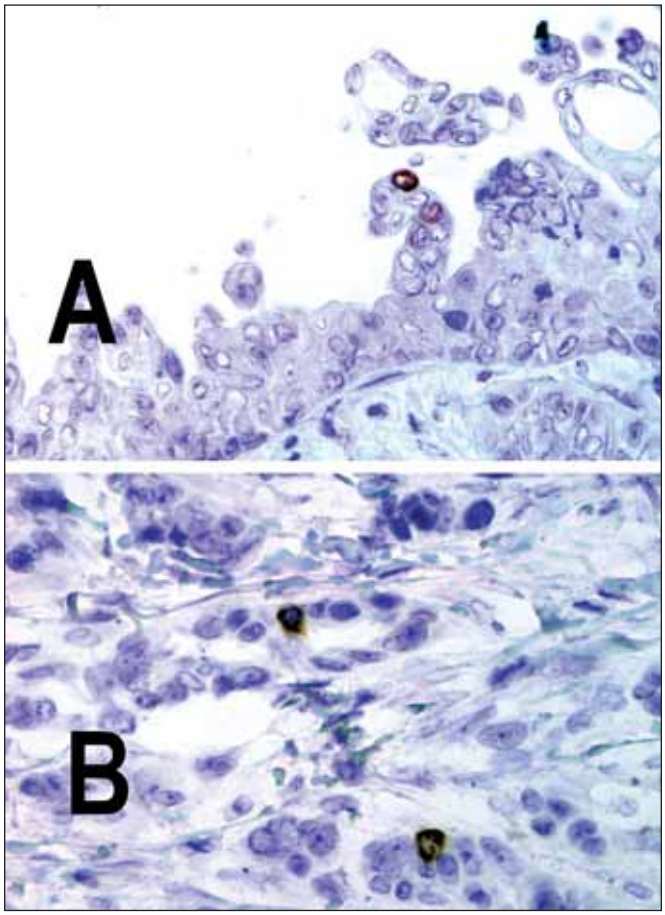

Fig. 2. A) Scattered positive cells for mammaglobin in one of the CAC cases (number 2)
B) A similar pattern was observed in four cases of metastatic carcinoma from the breast.

scattered cells expressing the antigen (Fig 2.B). In other five metastatic cases, positive cells were abundant and represented up to 60% of the tumoral cells (Fig.3). One case of meatastatic breast carcinoma did not show any expression of mammaglobin.

DISCUSSION

Our results lead us to conclude that a pattern of immunostaining with many positive cells for mammaglobin would favor a metastasis from breast duct carcinoma. With “many”, we mean a pattern of expression in which more than only scattered cells are stained. Although the definition might sound ambiguous, a posititivity of more than 10% of the tumoral cells sounds as a reasonable condition. On the contrary, a pattern of immunostaining with “few scattered positive cells only” would not favor any of the two possibilities, and the same would happen if there was no expression of the marker. With the limited number of CAC cases that we studied, one should be cautious before such conclusions can be categorized and more studies with the antibody would be necessary in the future.

Another limitation of our study is that all cases studied from breast were ductal carcinomas instead of the specific apocrine carcinoma of breast. Althought breast is considered by many as a modified apocrine gland (1, 2), it could be claimed that perhaps the expression of apocrine carcinomas of the breast would have been different. Nevertheless, some studies on the subject have demonstrated that “breast tumoral cells with both

Table 1: Details about the cases investigated for expression of mammaglobin

Case	Gender	Age (years)	Type of tumor	Variant	Location
1	Female	42	CAC	Tubular	Axilla
2	Female	62	CAC	Cribriform	Fossa poplitea
3	Female	63	ICB	Ductal	Skin of breast
4	Female	81	ICB	Ductal	Skin of breast
5	Female	70	ICB	Ductal	Pre-sternal area
6	Female	96	ICB	Ductal	Left axilla
7	Female	57	ICB	Ductal	Skin of breast
8	Female	75	ICB	Ductal	Skin of breast
9	Female	75	ICB	Ductal	Skin of breast
10	Female	56	ICB	Ductal	Skin of breast
11	Female	59	ICB	Ductal	Axilla
12	Female	74	ICB	Ductal	Left axilla

CAC: cutaneous apocrine carcinoma; ICB: infiltrating carcinoma of breast

apocrine and non-apocrine features express mammaglobin with roughly equal frequency and intensity" (39).

The information obtained gives us some help from the field of immunohistochemistry in a subject which is always difficult: the main differential diagnosis when facing a cutaneous apocrine carcinoma (CAC) is a metastasis from a breast carcinoma or also a carcinoma that arises in an axillary breast prolongation (17) or in ectopic mammary tissue (7, 20, 26, 35, 37, 39).

Some morphologic clues have been mentioned in literature in order to distinguish between both entities (32, 35), and one of the most helpful ones is the evidence of an in situ sweat gland component, which points out towards a CAC (9, 39). Since that finding is far from being the rule, the differential diagnosis between a primary tumor and a metastasis can sometimes be impossible without the appropriate clinical information (7, 20, 26, 35, 37, 39).

The immunophenotype of the tumor is only of a relative help in distinguishing its origin. In the past, some authors pointed out that an intense immunolabelling for CEA, especially in the absence of expression of GCDFP-15 by tumoral cells, would favour a primary cutaneous CAC over a metastasis from a breast carcinoma (20, 39). In fact, many of the CACs reported have shown a weak and focal expression of GCDFP-15 (26), or have failed to show any expression at all of the marker (7, 23, 24, 40). This is in spite of the fact that GCDFP-15 is considered as a very specific marker for apocrine differentiation (23, 39). Nevertheless, in a series, GCDFP-15 failed to mark four ductal breast carcinomas, while it was expressed by the only CAC studied (4), therefore demonstrating the relative use of the marker in this specific differential. Others demonstrated GCDFP-15 in less than half of their cases of breast carcinoma skin metastases (36).

It was sometime suggested that an immunophenotype androgen receptor (AR)+, estrogen receptor (ER)-, progesterone receptor (PR)-, would favour an apocrine origin (11, 25), since it is expressed not only by normal apocrine glands (11), but also by apocrine carcinomas (11, 22, 34) and by extrammary Paget disease, which is alleged by some to origin from apocrine glands (11). This latter point is nevertheless highly controversial, since the discovery of Toker cells also in the vulva (42). These cells are claimed as the precursor of extrammamary Paget disease by some (5, 15). An immunophenotype ER- PR- AR+ has not been the rule in all CACs studied in literature. Some for instance have demonstrated expression of ER in cribriform CAC (13). Some others have demonstrated expression of PR by apocrine adenomas, as well as by papillary CACs (23). Recently, Robson et al. studied a large series of CACs and demonstrated that 62 % were ER+, 60 % were PR+ and 36 % were AR- (30).

Cytokeratin (CK) 7 has been demonstrated as a good marker for Toker cells (14, 21, 41, 42) as well as for Paget disease, either mammary (26), or extrammary. It has not been found as useful in the diagnosis between a primary adnexal tumor and a metastasis, unless used as a part of an antibody panel (29). It is interesting how the pattern of immunostaining is important: focal CK7 expression was suggestive of a primary adnexal tumor, while diffuse immunostaining was mainly seen in a metastasis (29). This is similar to our results with mammaglobin, with a focal pattern favouring a primary tumor. This rule regarding CK7, nevertheless, seems to faint when distinguishing between CAC and a cutaneous metastasis of a breast carcinoma. CK7 has been demonstrated strongly and diffusely expressed by primary CAC (13).

Recently, p63 has been found to be of much use in the differential diagnosis of primary adnexal tumors versus metastatic adenocarcinomas to the skin (18, 19, 28).

However, CAC has been proved to be an exception, since not only its metastases but also the primary tumor does not express any p63 (19).

Other markers which are sometimes mentioned in the literature, in the diagnosis of primary cutaneous adnexal tumors, are only of relative help when facing a possible CAC. Cytokeratin (CK) 5/6, for instance, is usually expressed strongly and diffusely by primary cutaneous adnexal neoplasms (28). On the contrary, only a small percentage of cutaneous metastases express CK 5/6 and they usually do it in a weak way (28). Even so, these findings are not specific, and by no means CK 5/6 can be the only marker in which a diagnosis should be supported.

Mammaglobin is a 93 aminoacids protein which originally was identified in breast carcinoma cell lines (12). Mammaglobin is secreted as a glycosylated peptide (10). The expression of mammaglobin has been described in other

tissues apart from breast, like lung tumors, tumors from the female genital tract (16, 29, 33), salivary gland tumors (29), and malignant mesothelioma (8). Mammaglobin is also expressed by eccrine and apocrine sweat glands (12), but the expression is quite different from the one observed in breast tissue. While eccrine glands show strong cytoplasmic staining of the coiled cells, in the immunohistochemical study for mammaglobin, the apocrine glands showed only staining of scattered cells (31).

Logically, this pattern might be expected for adnexal tumors of apocrine origin. For instance, cylindroma has been negative in most cases in which mammaglobin has been investigated, and when positive, only a small group of cells expressed the marker (31). Apocrine hidrocystoma showed a pattern of staining similar to the normal apocrine gland, i.e. just some scattered cells were positive (31); and the same pattern was the one observed in hidradenoma papilliferum (31). This is quite different from the pattern of staining that is observed in the adenocarcinomas developing from the breast, in which an intense and diffuse expression for mammaglobin is quite the rule (38). CAC, on the contrary, has not been investigated till now for mammaglobin expression, to the best of our knowledge, but the differences in expression by the breast tissue and apocrine tumors make us think that it could be one of the first reliable markers in the differential diagnosis when facing a possible CAC.

Our results seem to indicate that some additional help in the differential diagnosis between these entities could be obtained from the use of this marker when facing difficult cases. This opinion is in a way contrary to what has previously been claimed in literature. Bhargava et al., for instance, asserted that “mammaglobin does not seem to be a useful stain to distinguish breast from sweat gland carcinomas” (6). Nevertheless, they do not specified the type of sweat gland carcinoma studied in their report. That information is important, not only because the CAC is the most difficult to distinguish from a metastasis, but also because mammaglobin is strongly expressed by the normal eccrine gland (31).

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HISTORIE PATOLOGIE

PROF. HLAVA V PARDUBICÍCH

Bohužel nedokonalé snímky z dob 1. světové války pocházejí z pardubické válečné nemocnice, která stála na místě dnešní čtvrti Dukla a přilehlých ulic, včetně jižní části nádraží.

Na prvém snímku je vlastní válečná nemocnice; šlo o obrovské zařízení pro 10 tisíc raněných a nemocných z celého tehdejšího Rakouska-Uherska. Zdravotnického personálu a vojáků tam sloužilo kolem 2800. Vedle desítek nemocničních baráků tu byly další budovy – operační sály, bakteriologie, patologie, lékárna a dále obrovská prádelna (sloužila pak přes 50 let pro pardubickou posádku) atd. Nemocnice měla i svoji železniční vlečku.

Neuvěřitelně masový nápor nemocných a raněných zaskočil všechny tehdy válčící státy především tím, že nastal kritický nedostatek odborného zdravotnického personálu, především lékařů.

Prof. Jaroslav Hlava (1855, Dolní Královice – 1924, Praha) byl jedním z odborníků, které tehdy úřady pověřily, aby vytvořili koncepci organizace obrovitého nemocničního areálu. Na druhém snímku je dvorní rada prof. Hlava, spolu s postaršími pány MUC. Fialou a MUC. Drábkem. Armáda tehdy zmobilizovala i takové, kteří kdysi absolvovali alespoň nějaký ten semestr medicíny; tito muži zastávali lékařská místa.

Na závěr připomeňme několik dat za života prof. Hlavy: již během studia na pražské lékařské fakultě začal pracovat na patologické anatomii u Edwina Klebse. Po promoci stážoval v Německu (u Rudolfa Virchowa) a ve Francii. Po rozdělení pražské Karlo-Ferdinandovy univerzity na českou a německou v roce 1882 se stal prvním přednostou českého patologického ústavu. Habilitoval se již v roce 1883 a řádným profesorem byl jmenován roku 1887, jako 32letý. Od roku 1897 až do své smrti byl předsedou Spolku českých lékařů. Po vzniku ČSR stál v čele Státní zdravotní rady. Zasloužil se o výstavbu moderního pracoviště patologie (1921) – dnešního Hlavova ústavu.

RNDr. M. Vostatek
Pardubice