THE UTILITY OF USUAL SERUM TESTS FOR THE PROGNOSIS OF PATIENTS WITH CUTANEOUS METASTASES

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ABSTRACT

Introduction. Cutaneous metastases are usually observed in end-stage cancers. In some cases, the diagnosis of skin metastases is not clinically evident. New studies have found that serological markers, such as fibrinogen and lactate dehydrogenase (LDH), represent predictive factors of cutaneous metastases and could be used in the follow-up.

The objective of our study was to evaluate these two markers (fibrinogen and LDH) and to find if there are any correlation between different parameters such as patients’ age, dimensions, and type of the tumour, as well as local complications.

Materials and methods. We conducted a retrospective study on 56 patients with cutaneous metastases. We analysed different parameters of patients who underwent skin biopsies or surgical excision, such as age,

RéSUMÉ

L’utilité des tests sériques habituels pour le pronostic des patients présentant des métastases cutanées

Introduction. Les métastases cutanées sont généralement observées dans les cancers en phase terminale. Dans certains cas, le diagnostic de métastases cutanées n’est pas cliniquement évident. De nouvelles études ont montré que les marqueurs sérologiques, tels que le fibrinogène et la lactate déshydrogénase (LDH), représentent des facteurs prédictifs de métastases cutanées et pourraient être utilisés dans le suivi.

L’objectif de notre étude était d’évaluer ces deux marqueurs (fibrinogène et LDH) et de rechercher s’il existe une corrélation entre différents paramètres tels que l’âge des patients, les dimensions et le type de tumeur, ainsi que les complications locales.
The utility of usual serum tests for the prognosis of patients with cutaneous metastases – BODOARCA et al

Introduction

Many studies have found that different serological markers, like fibrinogen and lactate dehydrogenase (LDH), can be considered prognostic factors for disease outcome and overall survival in metastatic disease, especially in pretreated end-stage cancers and those with first-line treatments. Fibrinogen is a glycoprotein synthesized by hepatocytes, with roles in acute phase inflammation and in tumour progression and metastasis development in different types of cancers, such as breast, lung, gastric, pancreatic, hepatocellular carcinomas, as well as in cutaneous squamous cell carcinoma and melanoma. Fibrinogen-related products are considered to have an important role in blood coagulation, tumour stroma formation and in hemostatic complications, especially in end-stage tumours, promoting migration of different types of cells, wound repair mechanisms and neovascularization. High levels of fibrinogen are known for their role as predictors in cardiovascular and chronic kidney disease.

Lactate dehydrogenase (LDH) is a well-known serum marker for cutaneous metastatic melanoma and was included in the staging guideline since the 2009 American Joint Committee on Cancer (AJCC) Staging Manual. LDH is important in the processes of glycolysis, the preferred mechanism of glucose metabolism of the tumour cells.

The prognostic role of LDH was studied for melanoma, but also for non-Hodgkin’s lymphoma, nasopharyngeal and breast carcinomas.

Cutaneous metastases are relatively uncommon, with an incidence ranging from 0.6 to 10% of all patients with malignancies. The most common tumours leading to skin metastases are melanomas,
both in men and in women, followed by breast carcinomas in women and lung carcinomas in men. Colorectal carcinomas can also frequently complicate with skin metastases.

**The objective of our study** was to analyse and characterize various types of cutaneous metastases and to highlight any possible correlations between different prognostic factors, such as patients’ age, tumours’ dimensions, fibrinogen and LDH levels, for a better understanding and prediction of the disease outcome.

**Materials and methods**

Fifty-six cases of cutaneous metastases were analysed. We collected data regarding the patients’ age, number and location of the metastases, diameters of the skin nodules, complications such as infection, ulceration, hemorrhage, and necrosis, and data about the tumour’s origin, type of neoplasia, existence of other metastases, malignancies, or associated diseases, as well as serum levels of fibrinogen and LDH.

All tumours were diagnosed in the Pathology Department of the University Emergency Hospital of Bucharest, Romania. The tissue samples were fixed with 10% buffered formalin and were processed by conventional histopathological method, using inclusion in paraffin and hematoxylin–eosin (HE) staining. Some of the cases were further analysed with immunohistochemical stains in other medical centres.

All the procedures and experiments of this study were in accordance with the ethical standards in the Helsinki Declaration of 1975, as revised in 2008, as well as the national law. The study was approved by the Ethics Committee of the University Emergency Hospital of Bucharest, Romania (approval no. 31673/01.07.2020). Written informed consent was obtained from all the patients included in the study.

Microsoft Excel for Data Analysis for descriptive statistics and regression coefficient for any presumable correlations were used, with a statistically significant p-value less than 0.05.

**Results**

The mean age of the patients was 63.57±14.73 years. 33 (57%) patients were women. The diameters of the analysed tumours ranged from 6 mm to 50 mm, with a mean value of 24.37±13.24 mm. 29 patients presented a single metastasis and 33 patients had multiple visceral and lymph node metastases. Half of the analysed cases (29 patients) presented local complications, such as necrosis, hemorrhage, ulceration, or infection.

Out of 56 cases, 28 patients were diagnosed with epithelial carcinomas, such as carcinomas or adenocarcinomas, 27 patients with melanoma (Fig. 1) and one with leiomyosarcoma. One patient was suspected of a neuroendocrine carcinoma or a multiple myeloma, needing further immunohistochemical (IHC) investigations.

The distribution of the primary tumour according to the histological type in women is presented in Table 1. Out of the 33 women patients, 13 were diagnosed with melanoma, 10 with breast carcinoma, two with serous ovarian carcinoma, two with gastric carcinoma, two with pancreatic adenocarcinoma, one with uterine cervix squamous cell carcinoma, one with uterine cervix adenocarcinoma, one with colonic adenocarcinoma, and one had leiomyosarcoma.

Of the 23 male patients, 14 had melanoma, 4 were diagnosed with colorectal adenocarcinoma, two were diagnosed with renal tumours, one patient presented with pulmonary squamous cell carcinoma (SCC), one with cutaneous SCC and one with unknown primary tumour, necessitating IHC.

The distribution of the primary tumour according to the histological type in men is presented in Table 2.

A total of eight patients were diagnosed with cutaneous metastatic adenocarcinoma. Five patients (71%) were known with colorectal neoplasia (two of mucinous type, two of NOS type and one with unspecified histological subtype) (Fig. 2, 3), two with pancreatic adenocarcinoma (NOS and clear cell subtype), and one with uterine cervix adenocarcinoma NOS type. The uterine cervix adenocarcinoma metastasis was diagnosed in a 63-year-old patient and...
presented as a single nodular tumour of 10 mm diameter localized near the umbilicus.

The metastases’ grade of differentiation ranged from well to poorly differentiated. The average age of patients with adenocarcinoma was 64.16 years, and the average dimension of the metastatic nodules was 22.93 mm. The serum levels of fibrinogen ranged from 163 mg/dL to 696 ml/dL, with an average value of 416.73 mg/dL. There were correlations between patients’ age and fibrinogen levels, and we determined a weak correlation between serum fibrinogen levels and dimensions of metastatic nodules ($r(7) = 0.36$, $p = 0.03$).

The distribution of cutaneous metastatic carcinomas according to the primary tumour was: from the 19 patients with carcinomas, 10 had breast cancers (6 with ductal type carcinoma, two with lobular carcinomas, one considered of NOS type and one as squamous cell carcinoma with breast origin), two had ovarian serous carcinoma, two had tubular and tubulo-cystic renal tumours, two had gastric carcinoma.

| Women | Uterin | Colon | Cutaneous | Gastric | Breast | Muscular | Ovarian | Pancreatic |
|-------|--------|-------|-----------|---------|--------|----------|---------|-----------|
| Adenocarcinoma | 1 | 1 | | 2 | |
| Mucinous | | | | | 1 |
| Not otherwise specified (NOS) | 1 | | | 1 | |
| Clear cell | | | | | 1 |
| Carcinoma | | 2 | | 9 | 2 |
| Ductal | | | | 6 | |
| Lobular | | | | 2 | |
| NOS | | | | 1 | 1 |
| Serous | | | | | 2 |
| Unknown | | | | | 1 |
| Leiomyosarcoma | | | | | |
| Melanoma | | | | 13 | |
| Unknown | | | | 7 | |
| Acral | | | | 1 | |
| Superficial spreading | | | | 1 | |
| Nodular | | | | 2 | |
| Polypoid | | | | 2 | |
| SCC | | 1 | | 1 | |
| Nonkeratinized | | 1 | | |

NOS - Not otherwise specified
SCC - Squamous Cell Carcinoma

Figure 2. Histological microscopy image of malignant proliferation composed of infiltrative cribriform structures suggesting an adenocarcinoma metastasis in the skin, HE 40x.

Figure 3. Immunohistochemical CDX2 (caudal type homeobox 2) staining of a colorectal skin metastasis, 40x.
and there was only one case of SCC of cutaneous, pulmonary and uterine cervix origin.

The average age of all these patients was 63.57 years. The average dimension of the metastases was 24.42 mm, and the average fibrinogen level was 434.51 mg/dL. Of all 56 patients, 27 patients had multiple cutaneous metastases, and 33 patients had visceral, osseous, retroperitoneal or lymph node metastases. 29 cases presented with local tumour complications, such as ulcerations, necrosis, or hemorrhage.

Table 2. The distribution of the primary tumours according to the histological type in men

| Men          | colon | colorectal | cutaneous | pulmonary | rectal | renal | unknown |
|--------------|-------|------------|-----------|-----------|--------|-------|---------|
| Adenocarcinoma | 2     | 1          | 1         |           |        |       |         |
| Unknown      |       |            |           |           |        |       |         |
| Not otherwise specified | 1 | 1 | | | | | |
| Mucinous     |       |            |           |           |        |       |         |
| Carcinoma    | 2     |            |           |           |        |       |         |
| Tubular      | 1     |            |           |           |        |       |         |
| Tubulo-cystic| 1     |            |           |           |        |       |         |
| Neuroendocrine carcinoma/myeloma | 1 | | | | | |
| Melanoma     | 14    |            |           |           |        |       |         |
| Acral        | 4     |            |           |           |        |       |         |
| Superficial spreading | 1 | | | | | |
| Nodular      | 7     |            |           |           |        |       |         |
| Unknown      | 2     |            |           |           |        |       |         |
| SCC          | 1     | 1          |           |           |        |       |         |
| Nonkeratinized | 1 | | | | | |

SCC - Squamous Cell Carcinoma

Figure 4. The correlation between fibrinogen and dimensions of the melanoma skin metastases.

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\text{r}(22) = 0.66; \ p < 0.004
\]
The most common localization of cutaneous metastases was the abdominal area. Breast carcinomas frequently metastasized on the anterior thorax (5 cases), 3 patients had cutaneous metastases on the extremities (axilla) and 2 cases metastasized on the scalp.

Of all patients with melanoma’s cutaneous metastases, 53% were males. 17 (males and females) had multiple cutaneous metastases and 14 presented with lymph node, osseous and pulmonary metastases. One patient had also salivary gland metastasis. The average
age of the patients with melanoma metastases was 62.11 years, and the average nodule diameter was 29 mm.

The average level of fibrinogen in melanoma patients was 459 mg/dL (in 24 cases), and the average LDH level was 251.71 IU/L. There were no correlations between the patients’ age and the dimensions of the metastatic nodules or between the age and fibrinogen values. We found, however, a moderate correlation between the levels of fibrinogen (high and normal) and the diameters of the metastases (r(22) = 0.66, p < 0.004) (Fig. 4), but no significant correlation between LDH and the metastatic nodules’ dimensions. Interestingly, we identified a moderate correlation between fibrinogen and LDH levels (r(10) = 0.67, p = 0.01), including patients with only high levels of the two serum markers (Fig. 5).

Moreover, we identified a strong negative correlation (Fig. 6) between the age of the melanoma patients and the high levels of LDH (r(4) = -0.81, p < 0.04), although the cohort examined included a small number of patients. Only eight patients from this study had elevated levels of LDH, of which five had melanoma metastases.

For non-melanoma patients, no correlation could be highlighted between the levels of LDH and fibrinogen, nor between the two parameters and age or diameters of metastatic nodules. As revealed also by other studies, the results of our study sustain that the high levels of fibrinogen could be considered an indicator of a poor prognosis, with metastatic potential, at least in melanoma patients.

**DISCUSSION**

Cutaneous metastases are uncommon findings in oncological patients, their incidence ranging between 0.5 and 10%8. The most frequent cancer metastasizing in the skin is melanoma, both in men and women, followed by breast, colorectal and lung carcinomas4,13,15. In our study, almost half of the examined metastases were of melanoma, both in men and women, data consistent with the literature. Furthermore, the second most frequent type of metastases diagnosed in female patients were from breast carcinomas, followed by gynecological tumours, gastric and pancreatic cancers. For men, the second most common diagnosed tumour was colorectal cancer, followed by renal tumours.

Interestingly, although uterine cervical tumours are known to rarely metastasize in the skin8, we identified two cases of cervix tumours, one adenocarcinoma and one SCC. The adenocarcinoma metastasis was located near the umbilicus, while the cervical SCC metastasized to the anterior thorax. Moreover, our group of study included two cases of renal carcinomas metastasized to the skin. These tumours are difficult to diagnose as skin metastases, because of their similarity to other cutaneous pathologies. Other two rare cases of pancreatic adenocarcinomas metastasizing in the skin were identified. Pancreatic carcinomas rarely metastasize onto the skin12,14,15, the umbilicus being the most frequent location, as observed in our study.

The mean age did not vary considerably between males and females, nor between the subcategorized groups. Half of the analysed metastases presented at least one complication.

Clinically, there is a wide variety of presentations of cutaneous metastases, from inflammatory aspects to nodules or cystic masses. They can mimic almost any skin pathology, being considered by some authors “great imitators”4,16. Histologically, they are frequently similar like the primary tumour, although a great number of cases can be classified as poorly or undifferentiated in comparison to primary tumours17. A careful examination will reveal, most of the time, the diagnostic criteria. Moreover, most of the patients are known with a primary cancer. Nonetheless, immunohistochemistry remains mandatory for a positive diagnosis and for differential diagnosis. We also had two cases in whom a clear and final diagnosis couldn’t be established without further IHC examination. One case raised the suspicion of a neuroendocrine carcinoma or multiple myeloma, and one case raised differential diagnosis problems between melanoma and leiomyosarcoma.

In our study, most melanoma metastases appeared on extremities, followed by thorax and abdomen, while breast carcinomas frequently metastasized on the anterior thorax, data consistent with the literature18.

We also analysed the serum levels of fibrinogen and LDH in the group of study. Fibrinogen is a 340 kDa glycoprotein synthesized by hepatocytes, fibroblasts and some epithelial and tumoral cells, involved in clot forming, acute phase inflammation and wound healing19. Moreover, high levels of fibrinogen are linked to cardiovascular diseases and chronic kidney disease6. Many tissues synthesize fibrinogen in inflammatory conditions, which further determines an inflammatory microenvironment for various tumours. Studies have showed that the levels of fibrinogen are also linked with tumour dissemination and size, metastatic potential, and tumour progression6, as well as with tumour progression, staging, metastases, and overall survival17,19,20. Fibrinogen increases the metastatic potential of circulating cells, sustaining adherence and survival of tumour cells in the newly formed vascularization, although it seems that it doesn’t impact the growth of existing metastases1. High levels of
fibrinogen were observed in various neoplasia, including lung carcinomas, gastric, hepatic, or gynecological tumours. In our study, we found a statistically significant correlation between the levels of fibrinogen (high and normal) and the size of metastatic nodules in melanoma patients. The group of patients with melanoma was the most relevant, because the number of cases was higher comparative with non-melanoma patients. One study emphasized the role of fibrinogen as a predictive factor in patients with diagnosed melanoma. LDH is an acknowledged prognostic marker for melanoma, both during pre- and post-treatment. High levels of LDH are correlated with a poor outcome in melanoma patients, and in those with breast and nasopharyngeal carcinomas. The mechanism behind LDH elevation in different types of cancers is explained by glycolysis pathway, namely by the Warburg effect. LDH converts pyruvate in lactate in the process of glycolysis, enhancing, thus, the anaerobic metabolism of the tumour cells, but it also maintains an inflammatory microenvironment, promotes angiogenesis, cell migration and metastasizing. In our study, LDH correlated with the patients’ age, as well as with fibrinogen levels, suggesting that LDH could be considered an indicator of a poor prognosis. The limitations of the study are related to the small sample size and its retrospective type.

CONCLUSIONS

Fibrinogen and LDH are two serological markers easy to measure in current medical practice. Fibrinogen and LDH levels correlate with each other and with others prognostic markers, such as patients’ age or dimensions of the metastatic nodules in patients with melanoma. There is a need for bigger studies to evaluate the interactions between malignant tumour cells and usual serological markers.

Author Contributions:

D.B., O.M.P. and M.C. contributed substantially to the conception and design of the study, the acquisition, analysis, and interpretation of the data, and were involved in the drafting of the manuscript. C.C.D. and S.B. contributed substantially to the analysis and interpretation of the data and were involved in the drafting of the manuscript. C.C.D. and M.C. were involved in the critical revisions of the manuscript for important intellectual content. D.B. and O.M.P. were responsible for confirming the authenticity of all raw data. All authors have read and approved the final manuscript.

Compliance with Ethics Requirements:

“The authors declare no conflict of interest regarding this article”

“The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study. The study was approved by the Ethics Committee of the University Emergency Hospital of Bucharest, Romania (approval no. 31673/ 01.07.2020). Written informed consent was obtained from all the patients included in the study”.

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