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Cancer metastasis of an unknown primary location into a postoperative kelody scar after a mine blast wound of the neck

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The connection between military trauma and cancer is not sufficiently studied. We present a clinical observation of metastasis of cancer of unknown primary localization into a keloid scar of the neck, which occurred after surgical treatment of a wound due to a previously suffered mine-explosive injury. There are no similar descriptions in the literature.

The aim of this article is analysis of a clinical case of adenocarcinoma metastases in keloid scar tissue, which occurred after gunshot wounds to the body.

Clinical observation. A young man, a military serviceman, developed a keloid scar after a landmine-explosive wound and primary surgical treatment of a neck wound, in which 2 years after excision, a metastasis of intestinal-type adenocarcinoma was detected (Cytokeratin-20+, Cytokeratin-7-, CDX-2+ and SATB 2+). With the help of clinical, endoscopic and radiological methods (computed tomography and positron emission tomography / computed tomography), the primary tumor and additional metastases in the neck, chest, abdominal cavity and pelvis could not be detected.

The article analyzes the possible mechanisms of the rare case of metastasis of adenocarcinoma in the tissue of an uninfected keloid scar and discusses the concept of the formation of a premetastatic niche in the early stages of carcinogenesis of a preclinical tumor.

Conclusions. This observation raises new questions for fundamental and translational studies of the process of hematogenous metastasis during the parallel progression of the primary tumor and its metastases.

Ключові слова: metastasis, adenocarcinoma, scar, keloid, military trauma.

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Метастаз раку невідомої первинної локалізації в операційний келоїдний рубець після мінно-вибухового поранення шиї

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Зв'язок між військовою травмою та раком вивчено недостатньо. У статті наведено клінічне спостереження метастазування раку невідомої первинної локалізації в келоїдний рубець шиї, що виник після хірургічної обробки рани внаслідок мінно-вибухового поранення. У доступній фаховій літературі не виявлено описів подібних клінічних випадків.

Мета роботи – аналіз клінічного випадку метастазування аденокарциноми у тканини келоїдного рубця, що виник внаслідок вогнепальних поранень тіла.

Клінічне спостереження. У молодого чоловіка, військовослужбовця, після мінно-вибухового поранення та первинної хірургічної обробки рани шиї виник келоїдний рубець. Через 2 роки після висічення у ньому виявлено метастаз аденокарциноми кишкового типу (Cytokeratin-20+, Cytokeratin-7-, CDX2+, SATB2+). За допомогою клінічних, ендоскопічних і радіологічних методів (комп'ютерна томографія та позитронно-емісійна томографія / комп'ютерна томографія) первинну пухлину та додаткові метастази у шиї, грудній, черевній порожнині та малому тазі виявити не вдалося. Проаналізовано можливі механізми рідкісного випадку метастазування аденокарциноми у тканини неінфікованого келоїдного рубця. Наведено концепцію формування преметастатичної ніші на ранніх стадіях канцерогенезу доклінічної пухлини.

Висновки. Описане спостереження ставить нові питання щодо процесу гематогенного метастазування під час паралельного прогресування первинної пухлини та її метастазів.

Keywords: метастаз, аденокарцинома, келоїдний рубець, військова травма.

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The relationship between military trauma and cancer is not well understood. In the literature there is a description of two cases of laryngeal cancer after a gunshot wound to the neck [1], basal cell carcinoma with metastases to the axillary lymph nodes in a man as a result of a gunshot wound to the shoulder [2], squamous cell skin cancer that arose in the scar after an old military wound [3].

There is a description of the accidental discovery of metastases of squamous cell carcinoma of unknown primary localization in the lymph nodes of the neck during emergency surgery for a gunshot wound [4].

We present a clinical observation of metastasis of cancer of unknown primary localization into a keloid scar of the neck that arose after surgical treatment of the wound as a result of a previous mine blast wound. A mine-explosive wound is the result of a simultaneous impact on tissue of the damaging factors of an explosive device that are heterogeneous in characteristics (shock wave, flame jet, mine fragments, etc.).

We have not come across a description of oligometastasis of adenocarcinoma of the intestinal phenotype in keloid tissue in the available literature.

Aim

Analysis of a clinical case of adenocarcinoma metastases in keloid scar tissue, which occurred after gunshot wounds to the body.

Material and methods

Morphological preparations of the removed keloid scar were examined after staining with hematoxylin-eosin. Monoclonal antibodies Cytokeratin-20 (DAKO, clone Ks 20.8), CDX-2 (DAKO, clone DAK-CD X2) and Tinto SATB 2 (monoclonal) were used for immunohistochemical research.

Colonoscopy, computed tomography (CT) and positron emission tomography-computed tomography (PET/CT) were used to find the primary location of the tumor.

Clinical case. Man L., born in 2002, a soldier of the Ukrainian Armed Forces, at the age of 20, received a mine-explosive fragmentation wound in the neck in March 2022. At the hospital, the bleeding was stopped and primary surgical treatment of the wound was performed. Almost immediately, a keloid scar formed *(Fig. 1)*, for the removal of which the patient went to the surgical clinic in February 2024, twenty-three months after the injury.

In soft tissue preparations of the excised scar, tumor growth with glandular-cribrotic structures and the presence of "dirty" comedonecrosis was detected. The tumor is represented by atypical monomorphic cells with an increased nuclear-cytoplasmic ratio. Normo- and hyperchromic nuclei in a state of pronounced atypical mitotic activity. Around the tumor complexes there is a pronounced desmoplastic reaction of the stroma, massive lymphohistiocytic infiltration with an admixture of neutrophils and the formation of lymphoid follicles. Thickened homogeneous eosinophilic collagen fibers are embedded in the desmoplastic stroma, which morphologically corresponds to their keloid transformation.

To clarify the diagnosis and determine the histogenesis of the tumor, an immunohistochemical study was performed. When using primary panel markers, it was found that tumor cells were positive for Pancytokeratin, Cytokeratin-20 and negative for Cytokeratin-7. The presence of a metastatic nature of adenocarcinoma was confirmed by a positive nuclear reaction to intestinal differentiation markers CDX-2 and SATB 2. Thus, the morphological structure of the tumor and the immunophenotype of its cells corresponded to metastasis of colon adenocarcinoma into a keloid skin scar *(Fig. 2, 3, 4, 5)*.

Subsequent endoscopic examination of the esophagus, stomach and colon revealed no intraluminal pathology.

According to CT data, there were no radiological signs of a tumor process in the chest, abdominal cavities and pelvis. Two metal fragments were found in the soft tissues of the neck *(Fig. 6)*. No additional pathological formations were found in the wound area.

Contrast-enhanced whole-body PET/CT was performed. F18DH was administered intravenously – 355.79999 MBq, effective dose of PET – 6.8000002 m^3, CT – 30.200001 m^3. At the time of the survey, no reliable data on the primary focus was obtained.

Signs of two single metabolically active lymph nodes in the upper part of the neck on the right were revealed *(Fig. 7)*.

A fine needle biopsy of a lymph node with a diameter of 0.8 cm yielded elements of lymphoid tissue without signs of malignant metastatic lesions. It was concluded that there were inflammatory rather than tumor changes. An excisional biopsy of two lymph nodes also showed no evidence of cancer. REA marker 2.01 ng/ml (normal value). The patient has no family history of cancer.

Thus, after surgery for excision of a keloid scar, oligometastasis of intestinal type adenocarcinoma (CD7-, CD20+) was accidentally discovered in the patient. It was not possible to establish the localization of the primary tumor using available methods.

The clinical diagnosis is formulated as TxNxpM1 (derma) – ICD-O code: 8140/6.

Considering the local nature of the lesion, it was decided to limit ourselves to excision of the metastasis without systemic antitumor therapy and active observation. When choosing this tactic, the patient's opinion was considered. Currently his condition is satisfactory. He makes no complaints.

Discussion

For a long time, hematogenous metastasis of cancer cells was considered a disordered process, "the height of chaos and randomness". However, back in 1889, the English surgeon Stephen Paget argued that the spread of a malignant tumor obeys strict biological laws. He proposed the "Seed and Sol" theory, according to which "organs cannot be completely passive and indifferent to the embolism of cancer cells". Paget explained it this way: "When plant seeds are dispersed in all directions, they can only germinate if they fall on favorable soil" [5].

This metastatic tropism, the "fatal attraction" of cancer cells to certain organs, remains one of the most intriguing questions in modern oncology, to which there is still no complete answer.

Isaac Fiedler, commenting on Paget's theory, said that "there is nothing random in biology, there are only processes that we do not understand" [6]. His work brought us closer to unraveling the mysterious and complex mechanisms of tumor metastasis [7].

The implementation of hematogenous metastases is a planned, targeted and well-prepared biological process in which not only a malignant tumor takes part, but also healthy tissues of the body. Metastatic cells colonize only those organs where a premetastatic niche has been previously prepared for them (from the Latin nidus – "nest") [8,9].

The premetastatic niche is a unique anomalous biological phenomenon that is designed to facilitate the adaptation of cancer cells to new conditions of existence. Without the process of its formation, the likelihood of metastases occurring is very low.

Niche formation is a multistep and complex process that begins long before cell colonization. The organs in which future metastases will develop are primarily exposed to selective influence of extracellular tumor vesicles and endothelial progenitor cells, which increase vascular

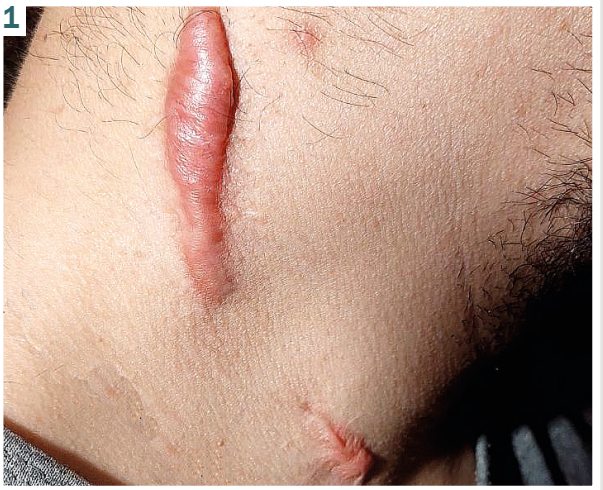


Fig. 1. Keloid scar of the neck that arose after surgical treatment of traumatic tissue damage due to a mine-explosive fragmentation wound.

Fig. 2. Metastasis of adenocarcinoma in the scar against the background of fibrous keloid tissue (hematoxylin-eosin staining).

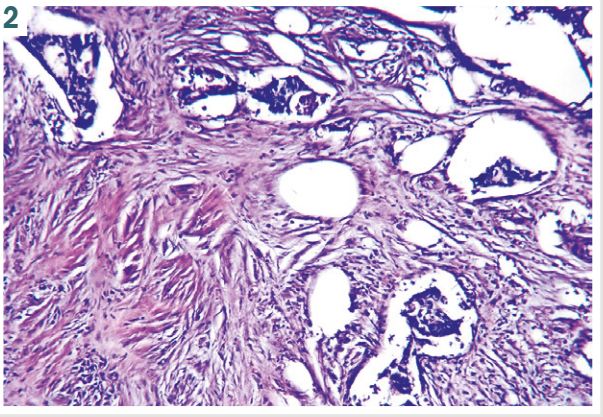
Fig. 3. IHC: positive staining of tumor cells with Cytokeratin 20 (DAKO, clone Ks 20.8).

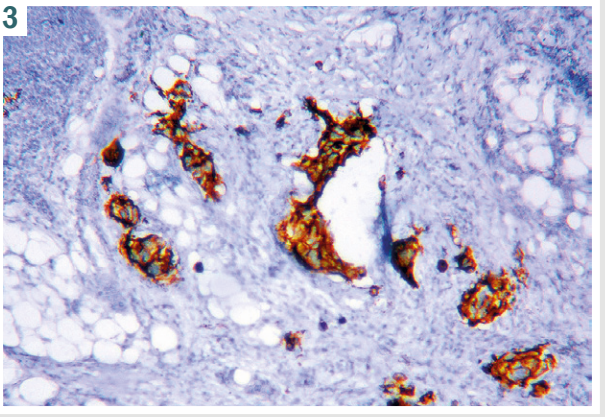
Fig. 4. IHC: positive nuclear staining of CDX-2 tumor cells (DAKO, clone DAK-CD X2).

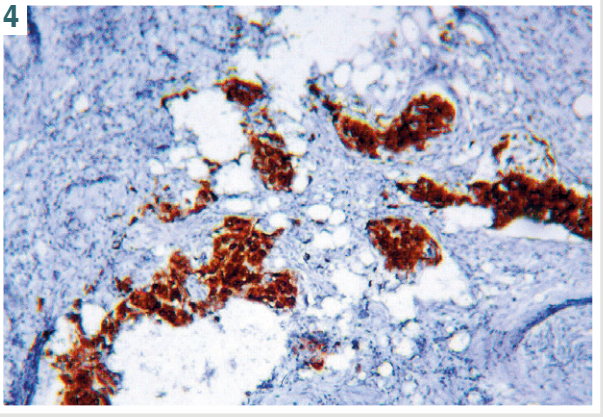
Fig. 5. IHC: positive reaction in tumor cells Tinto SATB 2 (monoclonal).

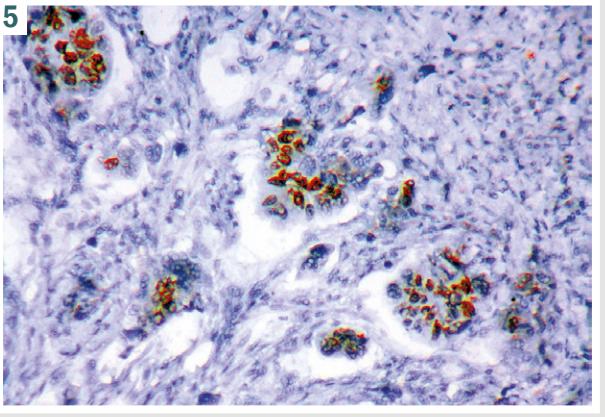
Fig. 6. CT scan: there are two metal fragments in the soft tissues of the neck.

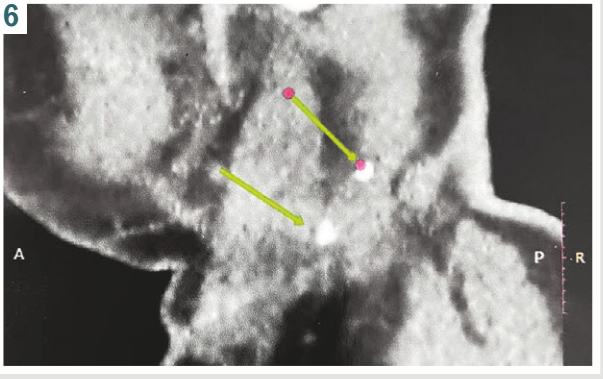
Fig. 7. Signs of two single metabolically active lymph nodes in the upper part of the neck on the right were revealed.

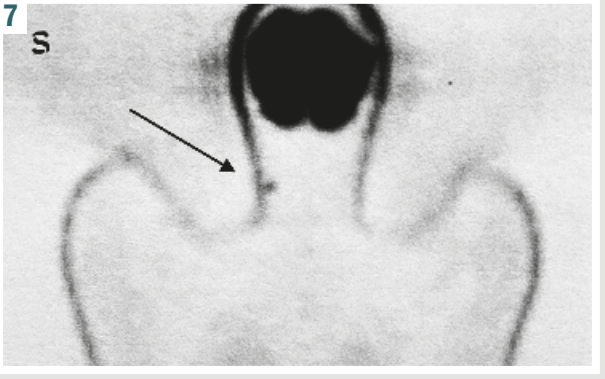












permeability in tissues, lead to degradation of the stroma and extracellular matrix, suppression and decrease in the activity of cells of the immune system [9].

In our observation, the function of a metastatic niche was performed by a skin keloid scar, which arose after surgical treatment of a mine-explosive fragmentation wound of the neck.

Metastases of visceral organ cancer to the skin are rare. They can develop in the navel in the form of a Sister Mary Joseph's knot [10], in surgical scars and in places of laparoscopic ports [11]. Metastases of pancreatic and colon cancer into surgical scars have been described 1–12 months after operations performed for a benign disease [12,13]. Metastases to the skin can appear after traumatic tissue damage, even if this area is located far from the primary tumor. Late metastasis of colorectal cancer to the skin of the upper lip of patient 14 was reported [14].

In extremely rare cases, as in our observation, skin metastases may be the first sign of visceral cancers (lungs, kidneys, ovaries), which have not yet manifested clinically [15].

Many evolutionary mechanisms in multicellular organisms that are involved in the process of rapid repair of epithelial damage are important for both wound healing and cancer cell proliferation [16].

Inflammation that occurs during regeneration appears to transform tissue following traumatic injury into a favorable microenvironment ("niche") for cancer cells and promote tumor growth. This process involves epithelial, endothelial, mesenchymal and immune cells, which interact through cytokines and growth factor signaling pathways [16,17].

Macrophages, platelets, neutrophils and myeloid suppressor cells play a major role in maintaining inflammation in the wound [18,19,20]. Subcutaneous fatty tissue in the wound can also influence tumor growth. For example, adipocytes play the role of an energy source for cancer cells by directly supplying them with lipids [21]. Fibroblasts, which are activated during inflammation, play a special role in wound healing and carcinogenesis. Cancer-associated fibroblasts are the main component of the stroma, providing conditions for tumor progression [22,23]. These cells produce the cytokine IL-6, which promotes tumor growth by stimulating angiogenesis, proliferation and invasion of cancer cells. Cytokines also have an inhibitory effect on immune cells, contributing to the formation of a suppressive microenvironment [24].

Postoperative keloid scar (χηλή – tumor and εἶδος – type) is an overgrowth of rough fibrous connective tissue of the skin. Excessively activated fibroblasts play an important role in the formation of keloids. The same processes provoke uncontrolled growth and proliferation of cells in cancer [25]. A postoperative keloid scar with excess fibrous tissue and excessive collagen deposition may provide an ideal niche for metastatic tumor cells. It is known, for example, that cancer often occurs against the background of fibrosis, an example of which is hepatoma growing in a cirrhotic liver.

Biologically, keloid and cancer are very similar. Both conditions are characterized by uncontrolled proliferation, progressive growth, invasion of surrounding tissues, neovascularization, lack of spontaneous regression, and extremely high relapse rates [26].

Keloid, like cancer cells, is characterized by the Warburg effect, which provides increased survival in hypoxic conditions, as well as other pathophysiological processes, for example, prolonged inflammation with increased levels of proinflammatory cytokines and transforming growth factor-β1 (TGF-β1) [27,28]. Keloid is a niche for stem cells [29]. However, keloids, unlike a malignant tumor, do not arise spontaneously and do not metastasize. They behave like localized aggressive benign skin tumors with excessive collagen production. There is a hypothesis that keloids may be one of the manifestations of paraneoplastic tumor syndromes [30].

Overall, parallels between keloids and benign and malignant mesenchymal tumors exist at the transcriptional, translational, cellular and tissue levels.

Although there is currently no direct evidence of the propensity of patients with keloids to develop cancer, one cohort study conducted in Taiwan found a higher risk of developing pancreatic carcinomas in people with keloids compared with the general population. The risk of cancer in the group of patients with keloids was 1.49 times higher compared to the control group [30].

Our observation is noteworthy in that the disease manifested itself as oligometastasis of adenocarcinoma of unknown primary localization into a post-traumatic keloid scar.

Approximately 50 % of all cases of prostate carcinoma are classified as well to moderately differentiated adenocarcinomas. In 30 % of patients in this group, poorly differentiated adenocarcinomas or undifferentiated carcinomas are diagnosed, in 15 % – squamous cell carcinomas, in 5 % – undifferentiated neoplasms. Synchronous metastases are usually detected in several organs (liver, lungs, lymph nodes, abdominal cavity, bones and brain) [31]. Oligometastasis is relatively rare.

In our case, the combination of cytokeratins CK7 (-) and CK20 (+) could only indicate carcinoma of the upper or lower gastrointestinal tract. Subsequent staining of tumor cells for organ-specific markers CDX-2 and Tinto SATB2 clearly indicated the localization of the tumor within the gastrointestinal tract, but it could not be detected using endoscopy and available radiological methods (CT, PET/CT).

Today, patients with metastatic malignant tumors of unknown primary location are divided into subtypes of favorable (20 %) and unfavorable (80 %) prognosis, depending on which various methods of local or systemic treatment are used [32]. Patients with oligometastatic disease belong to a clear favorable subtype [33].

The rule is that oligometastatic disease must be confirmed by radiological imaging, including PET/CT and MRI of the brain. In this case, there should be no diffuse tumor damage to organs (malignant pleural, peritoneal or leptomeningeal carcinomatosis). The number of metastases should not exceed five. Observations show that, regardless of tumor histology and organ affected by oligometastases, local treatment can be beneficial. Depending on the clinical situation, surgical removal, radiofrequency thermal ablation, or radiation therapy can be used [34].

These patients may have good long-term survival. There are no generally accepted recommendations for further monitoring of patients with oligometastases who have undergone ablative local therapy.

Since early diagnosis of local recurrence may allow repeat local treatment, further monitoring with CT or MRI is recommended at 3–6-month intervals for the first 2 years and then at 6–12-month intervals after 3 years [33].

This observation is of great theoretical significance, since it demonstrates that the metastatic potential of a malignant tumor occurs at the earliest preclinical stages of its development, which once again confirms the theory of parallel progression of the primary tumor and metastases, which was proposed by Christoph A. Klein in 2009 [35].

Conclusions

1. The detection of latent cancer, the first symptom of which was the appearance of a single metastasis in an uninfected keloid scar after surgical treatment of a mine-explosive fragmentation wound of the neck, has not yet been described in the literature

2. Keloid tissue in the skin, rich in activated fibroblasts and collagen, appears to be a convenient target for adenocarcinoma metastasis

3. This observation raises new questions for fundamental and translational research into the process of hematogenous metastasis of a malignant tumor

Prospects for further research. Prospects for further research are to study the influence of military trauma and wartime carcinogens on the risk of developing cancer in military personnel and the civilian population of Ukraine.

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