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Т.А. Гайдина*, А.С. Дворников, П.А. Скрипкина

Российский национальный исследовательский медицинский университет имени Н.И. Пирогова, Москва, Россия

ПАРАНЕОПЛАСТИЧЕСКИЙ СИНДРОМ ЛЕЗЕРА-ТРЕЛЯ (LESER-TRÉLAT): КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ, ДИАГНОСТИКА И ЛЕЧЕНИЕ

T.A. Gaydina*, A.S. Dvornikov, P.A. Skripkina

Pirogov Russian National Research Medical University, Moscow, Russia

Paraneoplastic Leser-Trélat Syndrome: Clinical Manifestations, Diagnosis and Treatment

Резюме

Осмотр кожного покрова — широкодоступный и простой метод обследования пациента, который, тем не менее, позволяет диагностировать системные нарушения и заболевания на ранних стадиях. Врач любой специальности может столкнуться в клинической практике с дерматологическими паранеопластическими синдромами, которые представляют собой группу кожных заболеваний, связанных со злокачественными новообразованиями, но не имеющих прямого отношения к первичной опухоли или ее метастазам. Своевременный анализ дерматологических паранеопластических синдромов позволяет заподозрить злокачественные опухоли, и срочно направить пациента к онкологу с целью ранней диагностики и лечения потенциально излечимого онкологического заболевания. В клинической практике достаточно часто встречается паранеопластический синдром Лезера-Треля (Leser-Trélat), который проявляется внезапным появлением множественных себорейных кератом (в основном, в области спины и живота) и увеличением их числа и размеров в течение небольшого промежутка времени (недели, месяцы). Лечение данного синдрома можно проводить как одновременно, так и после лечения основного злокачественного заболевания. Дерматологические паранеопластические синдромы требуют дальнейшего углубленного изучения для понимания патогенеза, создания четкой классификации и разработки алгоритмов действия врача.

Ключевые слова: *паранеопластические синдромы, дерматологические паранеопластические синдромы, синдром Лезера-Треля, кератома, множественные себорейные кератомы*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Examination of the skin is a widely available and simple method of examining the patient, which nevertheless allows you to diagnose systemic disorders and diseases in the human body at an early stage. A doctor of any specialty may encounter dermatological paraneoplastic syndromes in his practice, which are a group of skin diseases associated with malignant neoplasms, but not directly related to the primary tumor or its metastases.

*Контакты: Татьяна Анатольевна Гайдина, e-mail: doc429@yandex.ru
*Contacts: Tatiana A.Gaydina, e-mail: doc429@yandex.ru
ORCID ID: https://orcid.org/0000-0001-8485-3294

Timely analysis of dermatological paraneoplastic syndromes makes it possible to suspect malignant tumors that cause them and urgently refer the patient to an oncologist for the purpose of early diagnosis and treatment of a potentially curable oncological disease. In clinical practice, paraneoplastic Leser-Trélat syndrome is very common, which is manifested by the sudden appearance of multiple seborrheic keratomas (mainly in the back and abdomen) and an increase in their number and size over a short period of time (weeks, months). Treatment of this syndrome can be carried out both simultaneously and after treatment of the underlying malignant disease. Dermatological paraneoplastic syndromes require further in-depth study to understand the pathogenesis, create a clear classification and develop algorithms for the doctor's actions in case of their detection.

Key words: *paraneoplastic syndromes, dermatological paraneoplastic syndromes, Leser-Trélat syndrome, keratoma, multiple seborrheic keratomas*

Conflict of interests

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CPSs — cutaneous paraneoplastic syndromes, LTS — Leser-Trélat syndrome

Introduction

Skin examination is included in patient examination protocol of the vast majority medical specialties; it helps identify systemic disorders in the human body including undiagnosed malignant neoplasms. Cutaneous paraneoplastic syndromes (CPSs) are a group of skin diseases associated with malignant neoplasms, however, not directly related to the primary tumor or its metastases. It is important for any specialist to be aware of and be able to identify CPSs in order to suspect and diagnose the underlying malignant tumors as early as possible.

Cutaneous paraneoplastic syndromes

The studies demonstrate, that CPSs develop in about 7-15 % of patients with malignancies, while the development of CPSs can both precede the diagnosis of a malignant neoplasm, or start at the late stages of oncological process or be the first sign of relapse [1]. Timely diagnosis and correct interpretation of CPSs can provide earlier detection of malignant neoplasms and higher life expectancy of patients.

F. Hebra in 1868 was one of the first to suggest the hypothesis that sudden changes in skin pigmentation may be associated with a malignant process [2].

In 1976, Helene Ollendorff Curth proposed criteria for analyzing the relationship of dermatoses with other diseases including malignant tumors of internal organs. The criteria for CPSs diagnosis proposed by Curth are presented below:

1. Onset of dermatosis should coincide with the onset of a malignant disease.
2. Both processes develop simultaneously.
3. Dermatosis is not considered to be a part of a genetic syndrome.
4. Specific dermatosis is associated with a specific tumor.
5. Dermatoses rarely occur in general population.
6. Dermatosis is highly associated with a malignant disease [3, 4].

Not all six criteria are required to suggest an association between dermatosis and malignant disease. The first two criteria are sufficient to consider dermatosis as a process related to a malignant tumor. In 2010, Ortega-Loayza A.G. et al. proposed to distinguish between main and secondary criteria for CPSs defining [5].

There is no single generally accepted classification of CPSs. Most often, CPSs are classified according to their detection rate in certain malignant neoplasms, or to the clinical and morphological principles, or to known etiological mechanisms. Using the detection rate in certain malignant neoplasms, a number of national authors distinguish mandatory CPS (almost always associated with malignant neoplasms), optional CPS (the association is statistically predictable), and occasional CPS (the incidence in patients with malignancies is higher than in the general population) [6]. According to the detection rate in certain malignant neoplasms, foreign investigators divide CPS into two large groups: obligate and facultative [7, 8]. Obligate CPSs include rare dermatoses that are always associated with a malignant neoplasm. Facultative CPSs include more common dermatoses of various etiology; their onset as a paraneoplastic process was repeatedly reported in literature sources (Table 1) [8].

Leser-Trélat syndrome

Leser-Trélat syndrome (LTS) is a quite common obligate CPS in the practice of a general practitioner; it is manifested by the sudden onset of multiple seborrheic keratoses (mainly on back and abdomen) and by their increase in number and size during a short period of time (weeks, months) [9]. This syndrome was first described by French surgeons A. Leser and

Table 1. *Relationship of obligate and facultative dermatological paraneoplastic syndromes with malignant neoplasms*

Obligate dermatological paraneoplastic syndromes	Related malignancies
Paraneoplastic acrokeratosis (Bazex syndrome)	Squamous cell carcinoma (tongue, pharynx, larynx, esophagus, stomach, lungs)
Paraneoplastic pemphigus	Chronic lymphocytic leukemia, Castleman's disease, thymoma
Acanthosis nigricans maligna	Adenocarcinomas of the gastrointestinal tract
Hypertrichosis lanuginosa acquisita	Colorectal cancer, breast cancer, lung cancer
Necrolytic migrating erythema	Glucagonoma, small cell lung cancer
Leser-Trélat Syndrome	Gastric adenocarcinoma, colon cancer, lymphoproliferative diseases
Facultative dermatological paraneoplastic syndromes	**Related malignancies**
Erythema gyratum repens	Squamous cell carcinoma (esophagus, stomach, lungs)
Gangrenous pyoderma	Acute myeloid leukemia, myelodysplastic syndrome
Sweet-syndrome	Acute myeloid leukemia, cervical cancer
Dermatomyositis	Ovarian, lung and breast cancers
Pemphigoid of mucous membranes	Adenocarcinoma (colon, stomach, lungs)
Paget 's Extramammary disease	Urogenital and gastrointestinal carcinomas
Acquired ichthyosis	Hodgkin's lymphoma, carcinomas (lungs, ovaries, uterus)

U. Trélat in 1880 as the appearance of multiple skin angiomas with underlying malignant visceral tumor. In 1900, Hollander was the first to find the association of the appearance of multiple seborrheic keratoses with a malignant visceral tumor, however, the eponym remained as Leser-Trélat [2]. In 1916, Balo and Koprassi concluded that malignant processes were diagnosed three times as often in the patients with multiple seborrheic keratoses. Currently, there are descriptions of LTS in various malignant diseases, however, its pathophysiology is not completely understood. It has been proven that neoplastic cells can secrete factors similar to EGF-α (epidermal growth factor) that alter extracellular matrix, stimulate the growth of keratinocytes and contribute to the development of seborrheic keratosis [10]. Higher levels of transforming growth factor TGF-α were also found in the urine of a patient with LTS and melanoma [11].

According to national and foreign literature, more than 50 % of malignant neoplasms associated with LTS include adenocarcinomas of gaster [12], colon, rectum [13] and breast [14], however, LTS was also described by researchers in association with other underlying malignant neoplasms, including cancer of lungs [15, 16], kidneys [17], skin melanoma [18], cutaneous T-cell lymphomas [19]. Literature sources contain case reports, where LTS developed with no association with any malignant neoplasm [20] which contests the pertinence of LTS to the group of obligate CPSs.

The main clinical manifestation of LTS is the explosive onset or rapid increase in the size and number of seborrheic keratoses that are verrucous well-defined plaques of brown to black color located on the skin of chest, back, limbs, face, abdomen (Figure 1).

In LTS, numerous seborrheic keratoses are usually symmetrically arranged on the back resembling a "Christmas tree", "splash" or "raindrops" [21]. Patients with LTS can be of different age, however, the average age of the onset of this syndrome is about 61 years. There are no reports of any association of LTS with sex or race [22]. Special cancer alertness should arise in cases of young patients with no senile keratosis. The main subjective complaint of patients is itching, however, it is not mandatory. Dermoscopic signs of keratoses are as follows: comedogenic holes, hairpin vessels, cerebriform structures, milia-form cysts, moth-eaten borders, fingerprint-like structures (Figure 2).

Seborrheic keratoses is treated simultaneously or after the management of a malignant disease considering the fact that the number and size of keratoses may decrease during treatment [23]. The best method for removing keratoses is determined individually considering the characteristics of each patient. The most common methods are surgical excision, electroexcision, cryotherapy, destruction with neodymium or CO_2 laser. CO_2 laser destruction of keratoses is widely used (Figure 3, 4). This method minimizes thermal damage to healthy skin and allows obtaining a satisfactory aesthetic result. Applications of chemotherapeutic agents can be considered: 30 % prospidine ointment, 5 % 5-fluorouracil ointment, solcoderm, collodion with 10 % salicylic and lactic acid. Systemic retinoids are prospective agents in multiple seborrheic keratoses in young people [24]. After the removal of keratoses, patients with LTS should be followed-up for a long time in order to exclude a malignant process (Procedure for follow-up medical care for adults with malignancies, approved by order of the Ministry of Health of the Russian Federation of June 4, 2020 N 548n.).

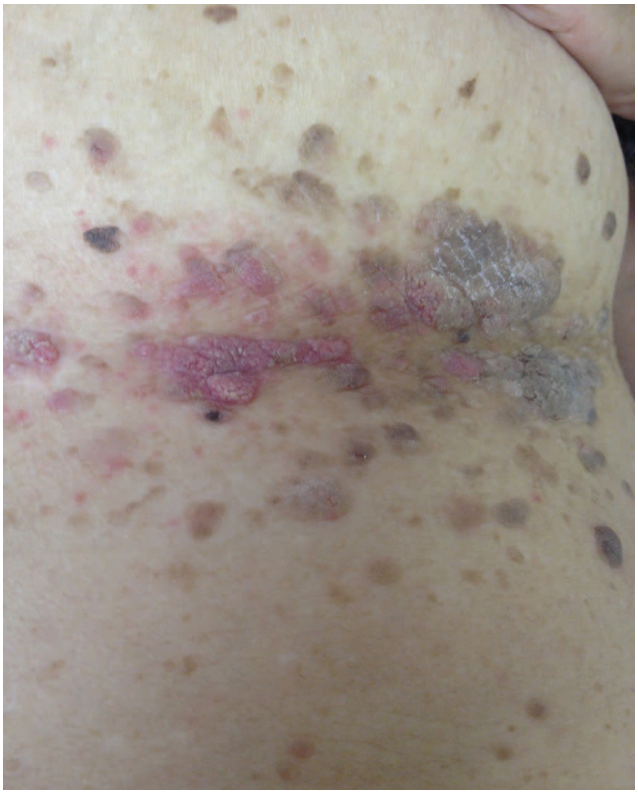

Figure 1. *Multiple keratomas on the body of a 68-year-old woman with rectal adenocarcinoma. Leser-Trélat syndrome.*

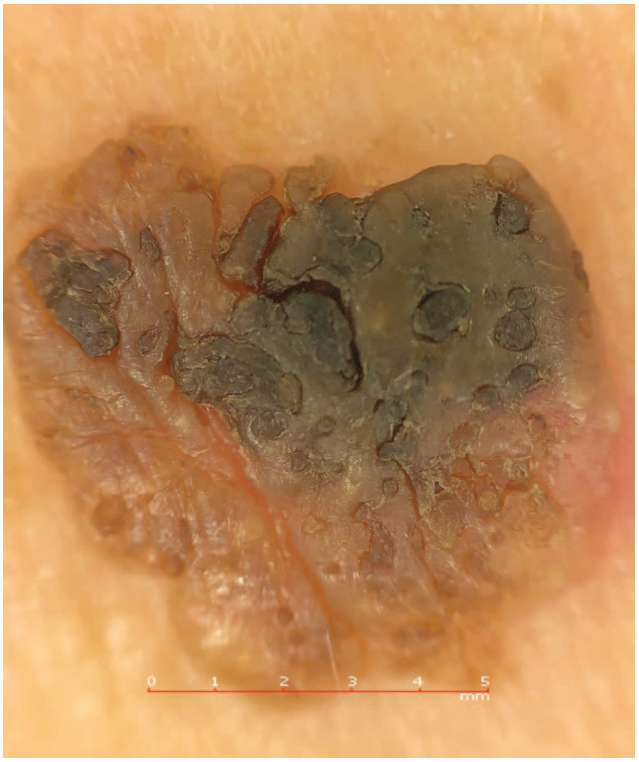

Figure 2. *The dermatoscopic picture of seborrheic keratoma is represented by thick brown pigment layers of varying intensity with hyperpigmented comedon-like holes (Magnification × 20)*

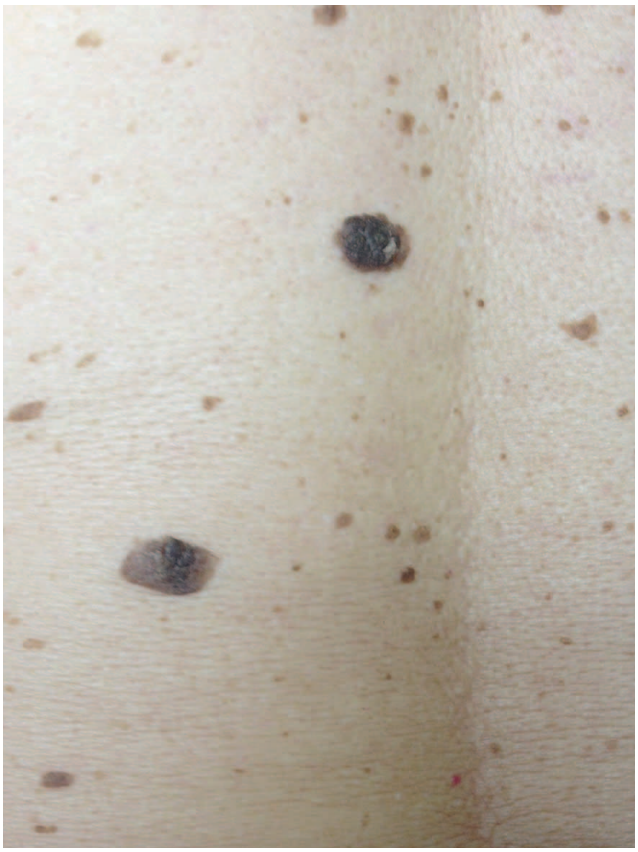

Figure 3. *Macro photograph of keratomas on the skin of a woman's back*

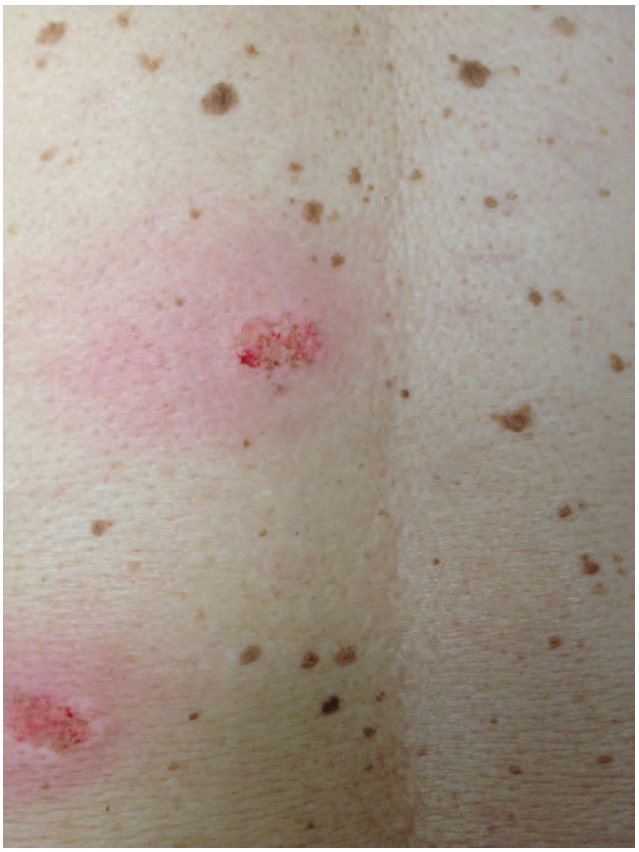

Figure 4. *Micrograph of a woman's back skin immediately after removal of keratoma with a CO_2-laser*

Conclusion

Multiple seborrheic keratoses may be encountered in the practice of any specialist including dermatovenerologists and general practitioners. One should consider that LTS is in most cases associated with a malignant neoplasm; therefore, a patient should be urgently referred to an oncologist for early diagnosis and treatment of a potentially curable malignancy. CPSs requires further advanced study in order to understand its pathogenesis, to create a clear classification, and to develop algorithms for physicians' actions.

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Гайдина Т.А. (ORCID https://orcid.org/0000-0001-8485-3294): сбор и обработка материала, написание текста, редактирование, окончательное утверждение рукописи для публикации

Скрипкина П.А. (ORCID https://orcid.org/0000-0003-2730-0938): написание текста

Дворников А.С. (ORCID https://orcid.org/0000-0002-0429-3117): обоснование и редактирование рукописи, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации

Contribution of Authors

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Gaydina T.A. (ORCID https://orcid.org/0000-0001-8485-3294): collected the data and performed the analysis, wrote the paper, edited the manuscript

Skripkina P.A. (ORCID https://orcid.org/0000-0003-2730-0938): wrote the paper

Dvornikov A.S. (ORCID https://orcid.org/0000-0002-0429-3117): edited the manuscript

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