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Morphogenesis of Changes in the Structural Components of the Skin in Cancer Patients with COVID-19 in Older Age Groups

Ekaterina S. Mishina, Mariya A. Zatolokina*, Alisa A. Yakovleva

Kursk State Medical University, Kursk, Russia

Abstract

Background: Immunosuppression caused by cancer or cytotoxic drugs, aging, and comorbidities makes cancer patients not only more susceptible to COVID-19, but also more likely to progress to a severe form and increase the incidence of serious complications. The epitheliotropy of this virus is of interest to the study of skin changes and the degree of their manifestation in patients with malignant neoplasms. In this regard, the aim of our research was to study the morphogenesis of changes in the structural components of the skin in cancer patients with COVID-19.

Methods and Results: We examined the features of morpho-functional changes in skin components in 80 cancer patients who died in Kursk and the Kursk region for the period January 2021–February 2022. Group 1 included cancer patients with no history of COVID-19, whose cause of death was peritonitis due to colorectal cancer; Group 2 included cancer patients whose cause of death was viral pneumonia caused by COVID-19. Each group was further divided by sex and age. The research material was skin fragments. The results of histological and morphometric studies of the skin show that lymphocytic infiltration was typical for all age subgroups of cancer patients with COVID-19, which had higher numbers of lymphocytes per 100 cells than cancer patients without COVID-19. Infiltrative-inflammatory changes are observed in the skin, the severity of which depends on the patient's age. For the age subgroup of 76-85 years without COVID-19, a more pronounced increase in the ratio of the reticular layer to the papillary layer was characteristic, due to a decrease in the thickness of the papillary layer. Pronounced thickening of the papillary layer was found in all age subgroups of cancer patients with COVID-19.

Conclusion: It is possible to predict more frequent skin manifestations in cancer patients who have had a new COVID-19 infection, the mechanism of which is mainly due to changes in specific leukocytes, T-lymphocytes, and macrophages and their infiltration of skin tissues.(**International Journal of Biomedicine. 2023;13(2):305-308.**)

Keywords: COVID-19 • cancer • skin • lymphocytes

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Introduction

The novel coronavirus infection (COVID-19) pandemic has forced the global scientific and medical community to urgently develop approaches to diagnosing, treating, and preventing pneumonia associated with a COVID-19 infection. Changes that occur in the cardiovascular, digestive, and nervous systems were also of greater interest. Over time, more and more attention has been paid to the study of dermatological manifestations, particularly due to concern for certain groups of patients, including those treated with immunosuppressants or immunomodulators. In addition, more and more data worldwide began to accumulate about skin manifestations of COVID-19, to one degree or another, occurring in almost every fifth patient and appearing more often for the first time four weeks from the onset of the main symptoms of COVID-19. Also, some authors point out that skin lesions can sometimes precede the main symptoms of COVID-19.[1-4]

It is particularly important to study the frequency of skin manifestations of COVID-19 in cancer patients and patients with immunosuppression since these categories of patients are at high risk for both the incidence of COVID-19 and the severity of its course.[5] The higher susceptibility of cancer patients to SARS-CoV-2 infection is either due to impaired immune responses characteristic of cancer and comorbidities, or to

***Corresponding author**: Prof. Mariya A. Zatolokina, PhD, ScD. Department of Histology, Embryology, and Cytology. Kursk State Medical University. Kursk, Russia. E-mail: marika1212@mail.ru*

specific therapies that alter immune homeostasis.[6] However, the structure of published descriptions of skin manifestations and analyses of risk factors, clinical course, and mortality in cancer patients infected with COVID-19 is currently heterogeneous regarding tumor formations. Data comparing cancer and non-cancer patients are scarce. The factors that make it relevant to study the morphogenesis of changes in the structural components of the skin in cancer patients under conditions of COVID-19 are (1) the high susceptibility of cancer patients to COVID-19 infection and their inclusion in the high-risk group, both in terms of incidence and severity of the infection; (2) the heterogeneity of published descriptions of the skin manifestations of COVID-19, and the paucity of data comparing cancer and non-cancer patients; and (3) the role of new data in improving the quality and timeliness of the diagnosis of COVID-19 and the skin damage caused by it.[7,8]

The study aimed to evaluate the morphogenesis of changes in the skin's structural components in cancer patients with COVID-19.

Materials and Methods

The practical part of our research included the study of cadaver material of 80 cancer patients who died in Kursk and the Kursk region, according to the Regional Pathological Bureau of the Kursk Region Health Committee for the period January 2021–February 2022. In this part, we examined the features of morpho-functional changes in skin components in cancer patients who had Covid-19. Excluded from the study were patients whose underlying disease was related to skin pathology and patients with severe somatic pathology. Patients were included in the study according to the selection criteria. They were divided into groups: Group 1 – cancer patients with no history of COVID-19, whose cause of death was peritonitis due to colorectal cancer, and Group 2 – cancer patients whose cause of death was viral pneumonia caused by COVID-19. Each group was further divided by sex and age (Table 1).

Table 1.

Distribution of patients according to age and sex.

Sex and age groups			n
Group 1	Women	65-75 years	10
		76-85 years	10
	Men	65-75 years	10
		76-85 years	10
Group 2	Women	65-75 years	10
		76-85 years	11
	Men	65-75 years	10
		76-85 years	9

The research material was skin fragments (2x2cm) taken along the midline of the abdomen, retreating 2 cm above the navel. The histological material was sent to the pathological laboratory. For light microscopy, the skin was fixed with 10% buffered neutral formalin and dehydrated in a frozen state in alcohols of increasing concentrations. For research, dehydrated samples were embedded in paraffin, and histological sections were made with a thickness of 4-5 μm. The sections were stained with hematoxylin and eosin (H&E) and examined in an Eclipse 80i direct light microscope, the objective magnification of which was x40, x200, and the eyepiece magnification x10. The thickness of the reticular and papillary layers, their ratio, the density of the connective tissue, and the number of interfiber spaces were determined using Altami Studio 3.0 and ImageJ 1.46h programs.

Statistical analysis was performed using the Statistica 10.0 software package (Stat-Soft Inc., USA). The mean (M) and standard error of the mean (SEM) were calculated. The Mann-Whitney U Test was used to compare the differences between the two independent groups. A probability value of $P \leq 0.05$ was considered statistically significant.

Results

After a morphological study of skin biopsies obtained from persons of Group 1 in all subgroups, the following changes were revealed: the epidermis consisted of five pronounced layers of epitheliocytes, and a rather small number of cells in a state of mitosis in the basal layer and a pronounced stratum corneum. The dermis was formed by a papillary layer, consisting of fairly thick collagen fibers with a small amount of amorphous substance. In the reticular layer, attention was also drawn to a large number of thickened collagen fibers with a small amount of elastic structures.

When studying skin biopsies obtained from males with COVID-19 in the age group of 65-75 years, we noted pathomorphological symptoms: the epidermis was represented by stratified squamous keratinized epithelium, covered with a slightly thickened stratum corneum. In the basal sections, a moderately pronounced lymphocytic infiltration was determined. Subepithelial (papillary dermis) showed signs of slight perivascular edema. The cellular composition was predominantly represented by fibroblastic different cells, lymphocytes, plasmocytes, and single mast cells. Attention was drawn to the increase in blood capillaries, compared with the control group. In the reticular layer there were thickened collagen fibers with pronounced interfiber spaces (Figure 1A).

When examining skin biopsies obtained from female COVID-19 survivors in the same age group, we found that the epidermis was enlarged with a spiny and granular layer. In the basal layer of the epidermis, there were a large number of melanocytes and lymphocytes. The papillary layer of the dermis was expressed, represented by a loose fibrous connective tissue consisting of thin collagen fibers. The cellular composition was represented by fibroblastic different cells, lymphocytes, macrophages, melanocytes, and mast cells. There were fewer blood capillaries, in comparison with biopsies obtained from males, and in the reticular layer, collagen fibers with pronounced interfiber spaces (Figure 1B).

When studying skin biopsy specimens obtained from males with COVID-19 in the age group of 76-85 years, we

found the surface relief to be smooth, due to the pronounced interstitial edema of the dermis. The epidermis was exhausted. A pronounced round cell infiltration was determined in the dermis's papillary layer. The layer itself had a small thickness. Numerous blood capillaries with dilated lumens were found. Around individual vessels, the marginal standing of lymphocytes and the exit of formed elements were determined. The reticular layer of the dermis was represented by relatively thin collagen fibers with large interfiber gaps and a large amount of amorphous substance (Figure 1C).

When studying skin biopsy specimens obtained from female patients who had COVID-19, in the same age group, we found the surface relief to be smooth, due to moderately pronounced interstitial edema of the dermis. The epidermis had focal thickened stratum corneum. Mildly expressed lymphoplasmacytic infiltration was also determined subepithelial (Figure 1D).

Thus, the results of histological and morphometric studies of the skin show that lymphocytic infiltration was typical for all age subgroups of cancer patients with COVID-19, who had higher numbers of lymphocytes per 100 cells (Table 2) than cancer patients without COVID-19. For the age subgroup of 76-85 years without COVID-19, a more pronounced increase in the ratio of the reticular layer to the papillary layer was characteristic, due to a change a decrease in the thickness of the papillary layer. Pronounced thickening of the papillary layer was found in all age subgroups of cancer patients with COVID-19, compared with the same age subgroups in cancer patients without COVID-19. A trend toward a decrease in the ratio of the cellular component to the intercellular substance was more typical for patients of all age subgroups in the group of cancer patients with COVID-19 (Table 2).

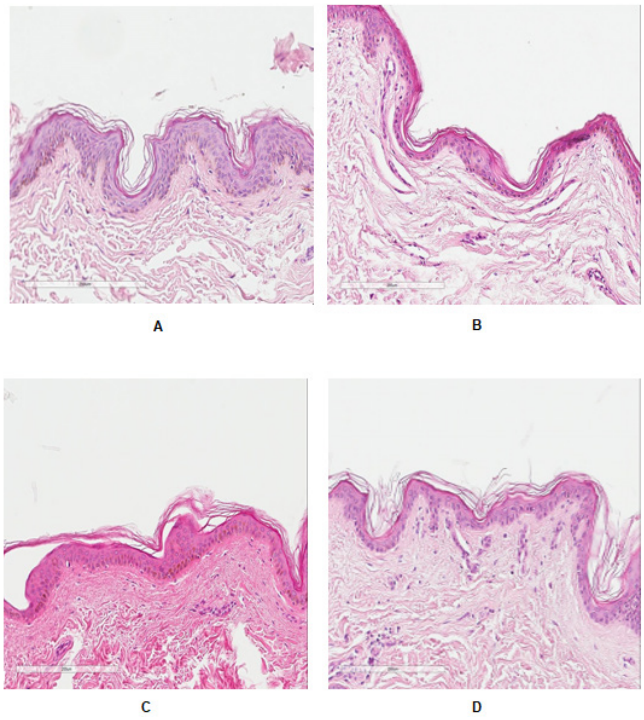

Fig. 1. *Skin fragments of cancer patients with COVID-19*

(A) A 71-year-old man; (B) A 77-year-old women; (C) A 70-year-old man; (D) A 78-year-old women. H&E staining; magnification, x200.

Conclusion

Based on the results of the study, it is possible to predict more frequent skin manifestations in cancer patients who have had a new COVID-19 infection, the mechanism of which is mainly due to changes in specific leukocytes, T-lymphocytes, and macrophages and their infiltration of skin tissues. The histological and morphometric data obtained during the study replenish the accumulated knowledge base, both about the skin features of infection with COVID-19, and about the features of its manifestations in cancer patients.

Table 2.
The quantitative data of the morphometric study

Variable	Group 1				Group 2			
	65-75 years		76-85 years		65-75 years		76-85 years	
	Men	Women	Men	Women	Men	Women	Men	Women
The number of lymphocytes per 100 cells	1.9±0.02	2.05±0.02	2.2±0.01	2.1±0.02	8.2±1.05*	7.42±0.9*	7.22±0.88*	7.02±0.82*
Thickness of the reticular layer, μm	4.8±0.3	5.1±1.02	4.91±0.8	5.4±0.5	9.12±1.52*	9.06±1.83*	9.44±1.38*	9.91±1.88*
Thickness of the papillary layer, μm	1.8±0.06	1.9±0.06	1.5±0.3	1.3±0.1	4.08±0.68*	3.49±0.76*	5.49±0.65*	4.1±0.69*
The ratio of the reticular layer to the papillary layer	2.6±0.03	2.7±0.01	3.2±0.02	4.2±0.01	2.23±0.03	2.6±0.01	1.72±0.04*	2.42±0.04
The ratio of the cellular component to the intercellular substance, %	94.7±2.2	89.6±1.2	90.51±3.74	96.3±2.9	84.69±3.27	84.18±3.20	86.57±3.74	87.31±3.87

** - P<0.05 in comparison with the corresponding subgroup of Group 1*

Competing Interests

The authors declare that they have no competing interests.

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