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Pathomorphological analysis of the qualitative composition of the inflammatory infiltrate around the pilosebaceous unit of the scalp in perifolliculitis capitis abscedens et suffodiens

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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

Perifolliculitis capitis abscedens et suffodiens (PCAS) or Hoffman's disease is considered a rather rare therapeutically complex purulent skin disease of unknown etiology. An active search for information regarding the qualitative and quantitative composition of the inflammatory infiltrate in PCAS, which could become a source for understanding the pathogenesis of this disease, revealed a lack of studies using the immunohistochemical staining method and authoritative recommendations on the interpretation of the obtained histological changes in punch biopsies for further treatment.

The aim of the work is to investigate the peculiarities of the location and number of CD20+, CD3+ cells and their populations of CD4+ / CD8+ T-lymphocytes of the inflammatory infiltrate around the pilosebaceous unit of the scalp in PCAS.

Materials and methods. In the work, the material of 12 male patients with a diagnosis of undermining abscessing perifolliculitis of the head (Hoffman's disease), aged from 20 to 51 years, the average age was 35.50 ± 11.54 years, and 5 samples of clean resection edges (conditional norm) of benign nevi of the scalp were examined. Heads of men aged 34 to 48 years, the average age was 32.10 ± 9.42 years (the control group compared with the research group did not show a statistically significant difference, $p > 0.05$). Immunohistochemical examination was performed according to the protocols of TermoScientific (TS) with primary antibodies against B-lymphocytes (CD20, RTU), T-lymphocytes (CD3, RTU), T-helper / T-regulatory cells (CD4, RTU), T-cytotoxic lymphocytes (CD8, RTU). Lab Vision Quanto imaging system (TS, USA) was used with detection of the reaction using DAB Quanto Chromogen (TS, USA).

Results. The pathohistological pattern of damage to the pilosebaceous unit of the scalp in PCAS is characterized by a deep inflammatory infiltrate located at the level of the reticular dermis or hypodermis, the development of perifolliculitis in the direction of the formation of deep abscesses and the destruction of follicles with the formation of lymphoplasmacytic granulomas or granulomas with giant cells, obligatory hyperplasia of the sebaceous apparatus glands that open into the hair follicle. Given the bactericidal and fungicidal properties of each fat that actively produces sebaceous glands, their hyperplasia in PCAS may be an indirect confirmation of an adaptive response to commensal biological factors in the development of this pathology. Accumulation of CD20 (+) cells in the outer root epithelial sheath and CD3 (+) cells in the outer and inner root epithelial sheath around the shaft of the hair follicle bud, which is a source of stem cells for reparative regeneration of the epidermis and epithelization of the wound surface, is likely to lead to long-term healing period and alopecia in PCAS. A high density of infiltration by CD20 (+) and CD3 (+) cells in the area of the excretory ducts of the sebaceous glands and CD3 (+) cells in the area of the secretory departments of the sebaceous glands probably leads to hyperplasia of the sebaceous gland apparatus as a reactive process of reparative regeneration in PCAS.

Conclusions. The predominance of $CD4^+$–T-helpers, compared to $CD8^+$–T-cytotoxic lymphocytes, among the CD3 (+) cells of the inflammatory infiltrate in PCAS indicates the superiority of the effector mechanisms of the immune response, which as a result leads to the activation of macrophages, neutrophils and CD20 (+) B-lymphocytes, which is reflected in the accumulation of these cells in the foci of chronic inflammation around pilosebaceous units of the scalp. The strong humoral response that develops in PCAS as a result of the activation of CD20 (+) B-lymphocytes through effector $CD4^+$–T-helpers is effective in the fight against extracellular microorganisms and their toxins and works most powerfully against microorganisms that have a capsule of polysaccharides and lipids, which become a target for antibodies produced by plasma cells, while the smaller number of $CD8^+$–T-cytotoxic lymphocytes are able to respond only to protein antigens. Thus, the study of the features of the immune response in PCAS indirectly helps to clarify the spectrum of etiological factors for improving the treatment strategy.

Keywords: abscessing perifolliculitis of the head, Hoffman's disease, dissecting cellulitis of the scalp, abscessing and undermining perifolliculitis of the head, cicatricial changes of the scalp, alopecia cicatrisata, dermatology, trichology, hair diseases, skin pathomorphology, immunohistochemistry, B-lymphocytes, T-lymphocytes.

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Патоморфологічний аналіз якісного складу запального інфільтрату навколо пілосебацеозної одиниці шкіри голови при підривному перифолікуліті голови з абсцедуванням

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Підривний перифолікуліт голови з абсцедуванням (англ. perifolliculitis capitis abscedens et suffodiens), який ще називають хворобою Гофмана (ХГ), є доволі рідкісним, терапевтично складним гнійним захворюванням шкіри невідомої етіології. Пошук інформації щодо якісного та кількісного складу запального інфільтрату при ХГ, що міг би стати кроком до розуміння патогенезу цього захворювання, показав брак досліджень, під час яких застосовували імуногістохімічний

Ключові слова: перифолікуліт голови абсцедуючий, хвороба Гофмана, розсікаючий целюліт шкіри голови, абсцедуючий і підривний перифолікуліт голови, рубцеві зміни волосистої частини голови, рубцева алопеція, дерматологія, трихологія, хвороби волосся, патоморфологія шкіри, імуногістохімія, В-лімфоцити, Т-лімфоцити.

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метод забарвлення, й авторитетних рекомендацій щодо інтерпретації виявлених гістологічних змін у панч-біопсіях для наступного лікування.

Мета роботи – дослідити особливості розташування й кількість CD20+, CD3+ клітин і їхніх популяцій CD4+ / CD8+ Т-лімфоцитів запального інфільтрату навколо пілосебацеозної одиниці шкіри голови при підривному перифолікуліті голови з абсцедуванням.

Матеріали і методи. Досліджено матеріал від 12 пацієнтів-чоловіків із діагнозом підривний перифолікуліт голови з абсцедуванням (хвороба Гофмана), віком від 20 до 51 років (середній вік – 35,50 ± 11,54 року), та 5 зразків чистих країв резекції (умовна норма) доброякісних невусів волосистої частини голови чоловіків віком від 34 до 48 років (середній вік – 32,10 ± 9,42 року). Пацієнти з групи контролю та групи дослідження за віком статистично достовірно не відрізнялися, $p > 0,05$. Імуногістохімічне дослідження здійснили за протоколами TermoScientific (TS) із первинними антитілами до В-лімфоцитів (CD20, RTU), Т-лімфоцитів (CD3, RTU), Т-гелперів / Т-регуляторних клітин (CD4, RTU), Т-цитотоксичних лімфоцитів (CD8, RTU). Використали систему візуалізації Lab Vision Quanto (TS, США) з визначенням реакції за допомогою хромогену DAB Quanto Chromogen (TS, США).

Результати. Для патогістологічної картини ушкодження пілосебацеозної одиниці шкіри голови при ХГ характерним є глибокий запальний інфільтрат, розміщений на рівні ретикулярної дерми або гіподерми, розвиток перифолікуліту в напрямі формування глибоких абсцесів і руйнування фолікулів з утворенням лімфоплазмоцитарних гранульом або гранульом з гігантськими клітинами, обов'язковою є гіперплазія апарату сальних залоз, що відкриваються у волосяний фолікул. Беручи до уваги бактерицидні та фунгіцидні властивості шкірного сала, що активно продукують сальні залози, їхня гіперплазія при ХГ може бути непрямим підтвердженням адаптивної реакції на коменсальні біологічні чинники розвитку цієї патології. Накопичення CD20 (+) клітин у зовнішній кореневій епітеліальній піхві та CD3 (+) клітин у зовнішній і внутрішній кореневій епітеліальній піхві навколо валика бруньки волосяного фолікула, що є джерелом стовбурових клітин для репаративної регенерації епідермісу та епітелізації ранової поверхні шкіри, імовірно, й спричиняє тривалий період загоєння й алопеції при ХГ. Висока щільність інфільтрації CD20 (+) та CD3 (+) клітинами в зоні вивідних протоків сальних залоз і CD3 (+) клітин у зоні секреторних відділів сальних залоз, імовірно, призводить до гіперплазії апарату сальних залоз як реактивного процесу репаративної регенерації при ХГ.

Висновки. Перевага $CD4^+$–Т-гелперів, порівняно з $CD8^+$–Т-цитотоксичними лімфоцитами серед CD3 (+) клітин запального інфільтрату при ХГ свідчить про перевагу ефекторних механізмів імунної відповіді, що в результаті призводить до активації макрофагів, нейтрофілів і CD20 (+) В-лімфоцитів. Це позначається на накопиченні цих клітин в осередках хронічного запалення навколо пілосебацеозних одиниць шкіри голови. Виражена гуморальна відповідь, що виникає при ХГ внаслідок активації CD20 (+) В-лімфоцитів через ефекторні $CD4^+$–Т-гелпери, є ефективною у боротьбі з позаклітинними мікроорганізмами та їхніми токсинами, найактивніше працює проти мікроорганізмів, що мають капсулу з полісахаридів і ліпідів, які й стають мішенню для продукованих плазмоцитами антитіл, а менш численні $CD8^+$–Т-цитотоксичні лімфоцити можуть реагувати тільки на білкові антигени. Отже, дослідження особливостей імунної відповіді при ХГ опосередковано допомагає визначити спектр етіологічних чинників для оптимізації лікувальної стратегії.

Perifolliculitis capitis abscedens et suffodiens (PCAS) or Hoffman's disease is considered a rather rare therapeutically complex purulent skin disease of unknown etiology, characterized by painful nodules, the formation of chronic abscesses, purulent fistulas and sinuses, resulting in progressive scarring alopecia and formation keloids on the scalp [1,2,3,4,5].

Due to the lack of a clear classification and terminology, as well as the untimely address of patients to specialists, it is difficult to determine the prevalence of this disease in the population [6,7,8].

In reports from economically developed countries, PCAS predominantly occurs in black men aged 20–40 years, often associated with adverse social conditions. As for Ukraine, the relevance of this disease has increased significantly over the past eight years against the background of an increase in men who are in difficult sanitary conditions due to military actions and constantly use protective equipment (helmets), which leads to long-term traumatization of the scalp, chronic inflammation and occlusion of follicles.

The clinical picture of PCAS has a rather specific appearance during the manifestation of the disease. The process is located mainly on the skin of the occipital and parietal areas of the head. The onset of the disease is determined by the presence of erythematous-papular and papular-pustular elements, which later transform into purulent nodules, which eventually form foci of atrophic changes, which is the main cause of cicatricial alopecia [9,10,11,12].

An active search for information on the qualitative and quantitative composition of the inflammatory infiltrate in PCAS, which could become a source for understanding the pathogenesis of this disease, revealed a lack of studies using the immunohistochemical staining method and authoritative recommendations on the interpretation of the obtained histological changes in punch biopsies for further treatment. In addition, many researchers note that reliable randomized control trials are also urgently needed to determine the most effective approaches to the treatment of PCAS, because the therapy of this debilitating dermatosis is difficult due to the relapsing nature of the course [2,7,13].

Starting from the third month, the development of hair is initiated in the skin due to the ingrowth of the epidermis deep into the dermis. Epithelial growth is stimulated by special mesenchyme cells that form hair papillae. Simultaneously with the development of hair, the formation of sebaceous glands occurs, the secretion of which (sebum) forms a syrupy film on the surface of the fetal skin and protects it from maceration. The morphogenetic, anatomical and functional connection of the hair root with the apparatus of the sebaceous gland logically formed the term – "pilosebaceous unit", which in the context of this pathology should be considered as the smallest unit of damage [8].

Aim

To investigate the features of the location and number of CD20+, CD3+ cells and their populations of CD4+ / CD8+ T-lymphocytes in the inflammatory infiltrate around the pilosebaceous unit of the scalp in PCAS.

Materials and methods

The paper examines the material of 12 male patients with a diagnosis of PCAS in the erythematous-papular or suppurative stage, who were examined and treated at the Medical Center of the Private Enterprise "Dzerkalo" (Dnipro, Ukraine). The age of the patients ranged from 20 to 51 years; the average age was 35.50 ± 11.54 years. The diagnosis was made based on clinical, anamnestic, laboratory (clinical and biochemical blood tests), instrumental (trichoscopy and dermatoscopy), microbiological and pathomorphological studies (puncture punch biopsy with histological examination in stained hematoxylin-eosin). For the control group, 5 samples of clean resection edges (conditional norm) of benign nevi of the scalp of men aged 34 to 48 years were selected, the average age was 32.10 ± 9.42 years (in comparison with the study group, no statistically significant difference was found, $p > 0.05$).

The study was approved by the commission on biomedical ethics of the Dnipro State Medical University (based on the extract from the minutes of Meeting No. 3 dated 16 November 2022) and was conducted in accordance with the written consent of the patients and in accordance with the principles of bioethics set forth in the Helsinki Declaration "Ethical Principles of Medical Research Involving Humans" and the "Universal Declaration of Bioethics and Human Rights (UNESCO)".

Histological method. 12 formalin-fixed and paraffin-embedded blocks of puncture punch biopsies of patients with PCAS and 5 formalin-fixed and paraffin-embedded blocks of the conventional norm (clean resection edges of benign nevi) were taken from the archive of CE "Dnipropetrovsk Regional Clinic Hospital named after I. I. Mechnikov", in the period from April 2023 to February 2024. In all cases, diagnostic and morphological features were evaluated and confirmed by repeated examination by two independent pathologists. Sections with a thickness of 4 μm were made on a Microm HM-340 microtome, stained according to the standard method with hematoxylin and eosin [14].

According to the histological structure, all observations were presented by the skin of the scalp, which corresponded to the structure of thin skin with long hair, for the possibility of assessing structural disorders with the development of cicatricial alopecia, biopsies were selected for further immunohistochemical staining, including 2 or more pilosebaceous units (hair together with adjacent sebaceous glands).

Immunohistochemical method (IHC). Immunohistochemical staining was performed according to the protocols of TermoScientific (TS) with primary antibodies against B-lymphocytes (CD20, RTU), T-lymphocytes (CD3, RTU), T-helper / T-regulatory cells (CD4, RTU), T-cytotoxic lymphocytes (CD8, RTU). The Lab Vision Quanto visualization system (TS, USA) was used with reaction detection using DAB Quanto Chromogen (TS, USA) [15].

According to the recommendations of D. E. Branisteanu et al. (2009), the presence of an inflammatory infiltrate was evaluated in the area of the epidermal-dermal junction, in various structures of the pilosebaceous unit, perivascular, and separately in the departments of sweat glands. At the same time, the immunoreactivity of CD20 and CD3 markers was evaluated as follows: (–) – negative, without staining or background brown staining in non-specific areas of cells, (+) – staining of membranes, or membranes and cytoplasm of cells with the calculation of the number of cells in the field of view of the microscope (×400) [6]. To obtain digital photos, a Zeiss Primo Star microscope camera – Axiocam ERC 5s with licensed software ZEN 2 blue edition was used.

Statistical analysis was carried out in the software environment R version 3.4.1 (2017-06-30); the R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit) under the GNU General Public License. The significance of intergroup relationships by quantitative distribution was determined using Fisher's exact test. The difference between subgroups was considered probable at $p < 0.05$ [16].

Results

The main morphological manifestations of damaged areas of the scalp (thin skin with long hair), where biopsy samples were obtained, stained with hematoxylin and eosin, showed abscessation, melting of the connective tissue of the dermis with granulomatous inflammation, which resembled a reaction to a foreign body (the formation of giant cells of the "foreign body" type). Macroscopically, this corresponds to areas of conglobate acne and cicatricial alopecia of the scalp with recurrent inflammatory nodules on the surface of the alopecia plaques and follicular pustules at their margin. The multilayered flat epidermis of these areas was moderately acanthotic, with perivascular and perifollicular lymphoplasmacytic infiltrates were always observed in the dermis *(Fig. 1a)*. Separately, it is necessary to note hyperplasia of the sebaceous glands, which was also accompanied by chronic inflammatory infiltration with a predominance of plasma cells *(Fig. 1b)*, follicular hyperkeratosis, blockage and dilatation of their lumens *(Fig. 1c)*.

However, the very dense infiltrate did not allow us to assess the qualitative composition of the cells. Therefore, we performed an IHC study to detect B-lymphocytes (CD20 (+) cells), T-lymphocytes (CD3 (+) cells), and their subpopulations, namely, CD4 (+) and CD8 (+) cells.

But the very dense infiltrate did not make it possible to assess the qualitative composition of the cells. Therefore, we conducted an IHC study to detect B-lymphocytes (CD20 (+) cells), T-lymphocytes (CD3 (+) cells), and their subpopulations, namely, CD4 (+) and CD8 (+) cells. Evaluating the distribution and accumulation of CD20 (+) cells (B-lymphocytes), which ensure the production of antibodies and support the local humoral response to damage, it is necessary to note their uneven distribution around and in hair follicles and the tendency to form very dense clusters of the granuloma type *(Fig. 2)*. Many

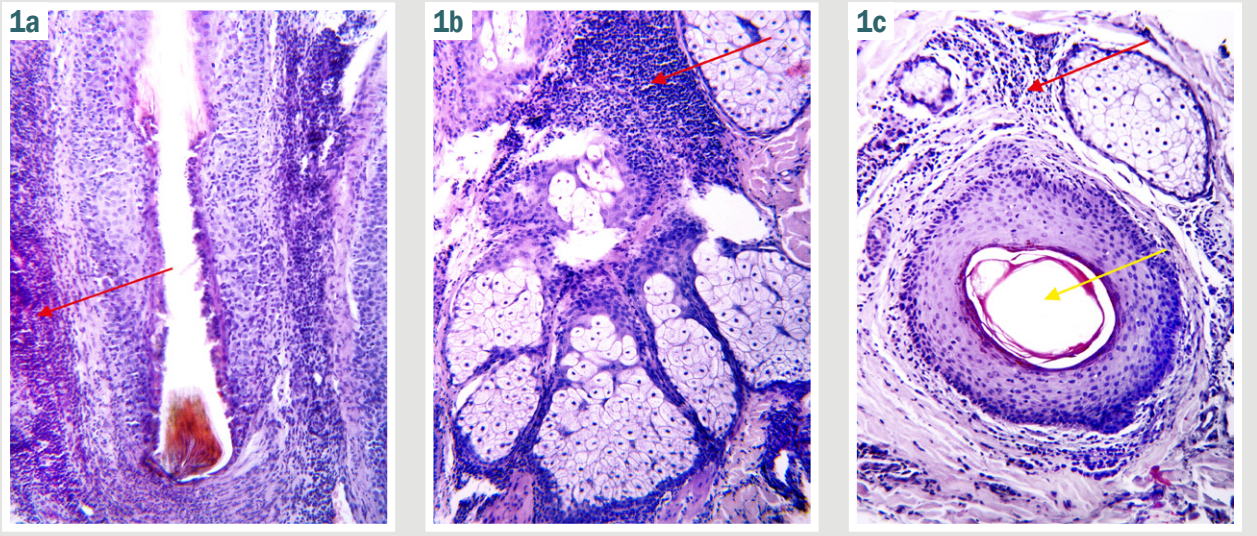

Fig. 1. Layers of the deep dermis and subcutaneous tissue of the hairy part of the head, stained with hematoxylin and eosin (×200). **a:** intense granulomatous inflammation (red arrow) around a hair follicle containing a small remnant of the hair shaft, with accumulation of plasma cells (mostly), lymphocytes, epithelioid cells, and foreign body type giant cells; **b:** hyperplasia of the sebaceous glands with massive inflammatory infiltration in the area of the ducts (red arrow); **c:** horizontal section of a hair follicle with dilatation (yellow arrow), the inflammatory infiltrate is denser on the side of the follicle facing the sebaceous gland (red arrow).

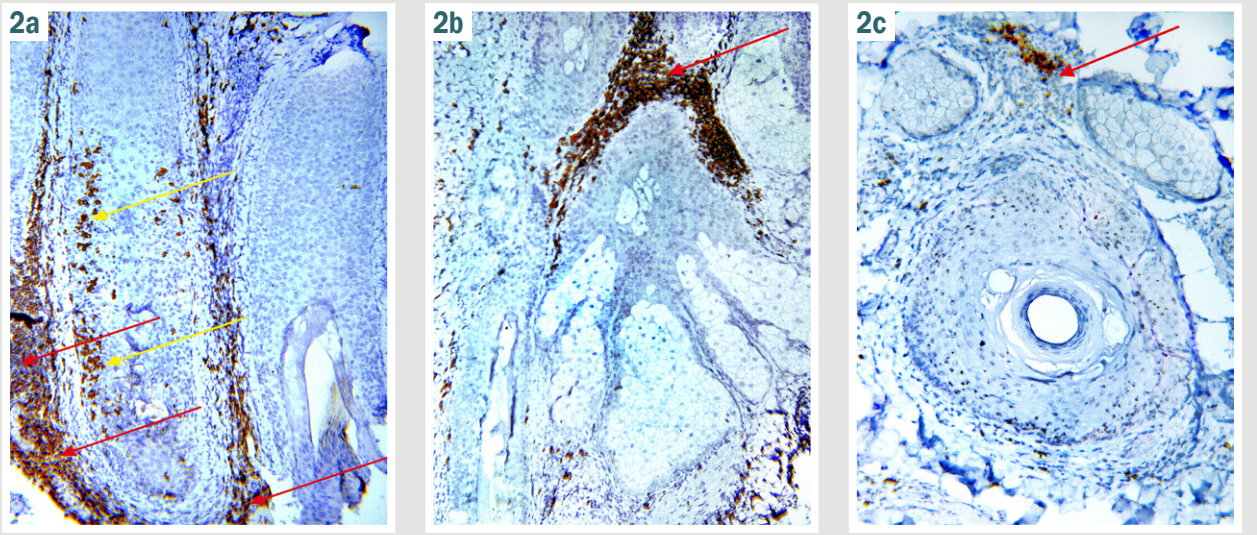

Fig. 2. Layers of deep dermis and subcutaneous tissue of scalp areas, reaction of inflammatory cells with the CD20 marker, IHC method with Mayer's hematoxylin (×200). **a:** dense clustering of CD20 (+) cells around the dermal pouch of the hair follicle (red arrows) and in the outer root epithelial sheath (yellow arrows); **b:** accumulation of CD20 (+) cells around the excretory ducts of the sebaceous glands (red arrow), characterized by significant hyperplasia; **c:** infiltration by CD20 (+) cells has a greater density precisely in the area of the sebaceous gland and generally decreases in the upper parts of the dermis.

CD20 (+) cells was detected in the connective tissue around the dermal bag, which forms the hair dermal papilla (protrusion of loose connective tissue at the base of the hair root) and ensures the production of growth regulators and cyclic changes in the hair follicle *(Fig. 2a, red arrow)*.

Another center of accumulation of CD20 (+) cells was found in the outer root epithelial sheath *(Fig. 2a)*, especially in the middle third of the hair follicle, where the hair follicle bud ridge is located (local thickening of the outer root sheath near the attachment of the hair straightener muscle). Probably, B-lymphocytes penetrate there from the outside through the vitreous membrane (thick basement membrane), which should separate the connective tissue of the dermal bag from the epithelial structures of the hair follicle, or at the bottom of the hair follicle, where the outer root epithelial sheath is very thin and consists of only one layer of epithelial cells. Due to damage to the area of the shaft, hair growth and its restoration stops.

Additionally, a significant accumulation of CD20 (+) cells was found around the excretory ducts of hyperplastic sebaceous glands, short and wide tubules lined by stratified epithelium and opening into hair follicles *(Fig. 2b)*. The infiltrate of CD20 (+) cells was preserved in large cells around the follicles and seemed almost homogeneous, but if we analyzed the distribution of CD20 (+) cells in the horizontal plane, it turned out that the accumulation of B lymphocytes had a greater density in the area of the sebaceous glands, and judging by the layer-by-layer sections increased from top to bottom *(Fig. 2c)*.

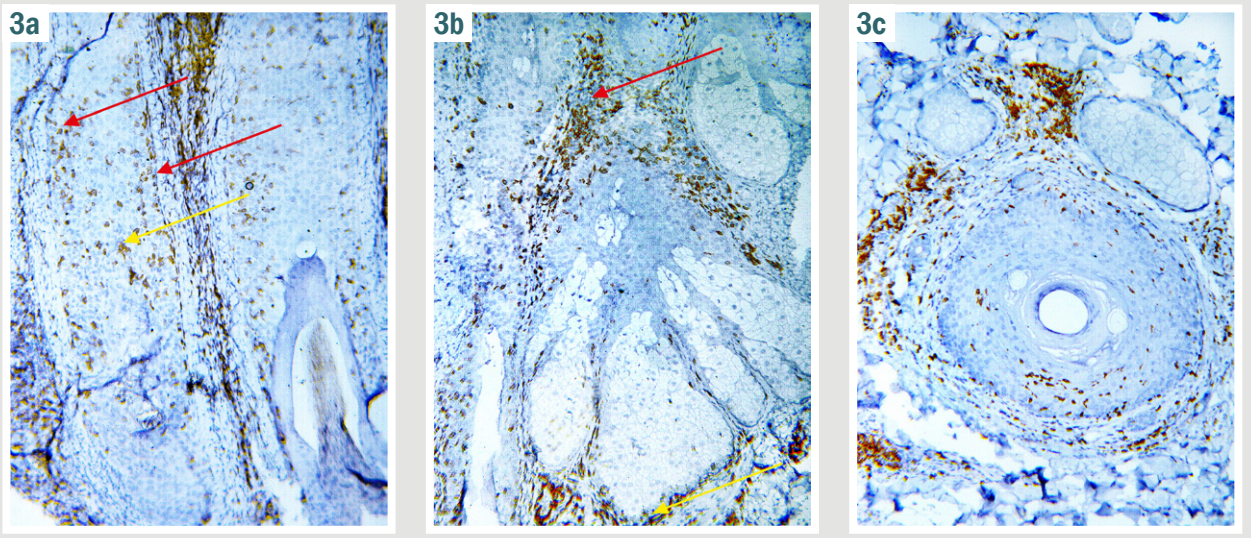

Fig. 3. Layers of deep dermis and subcutaneous tissue of scalp areas, reaction of inflammatory cells with CD3 marker, IHC method with Mayer's hematoxylin (×200). **a:** diffuse arrangement of CD3 (+) cells along the hair follicle, in the outer root epithelial sheath (red arrows) and focally in the inner root epithelial sheath (yellow arrow); **b:** accumulation of CD3 (+) cells around the excretory ducts of the sebaceous glands (red arrow) and secretory compartments with infiltration of the basal layer of cells (yellow arrow); **c:** infiltration of CD3 (+) cells has a greater density in the upper parts of the dermis, compared to CD20 (+) cells.

The control group was characterized by the absence of CD20 (+) cells in the structures of the hair follicle with the sebaceous gland and the surrounding areas, instead, single B-lymphocytes (2–3 CD20 (+) cells in the field of view at a magnification of ×400) were found in the stroma between the vessels and at the border epidermal-dermal junction.

The distribution of CD3 (+) cells (T-lymphocytes) mostly repeated the accumulation of CD20 (+) cells (B-lymphocytes) but had a lower density of infiltration in the granulomas of the hypodermis around the hair follicles, instead, it was denser in the upper parts of the dermis and the basal layers of the epidermis *(Fig. 3)*.

The accumulation of CD3 (+) cells in the outer root epithelial sheath turned out to be more significant, compared to CD20 (+) cells, and was more evenly distributed along the entire length of the follicle from top to bottom, with the involvement of the inner root epithelial sheath *(Fig. 3a)*, which is not was characteristic of CD20 (+) cells.

It should be noted that CD3 (+) cell infiltration of the sebaceous glands was found not only around the excretory ducts but also in the secretory departments (glandular sacs) located on the border of the papillary and reticular dermis layers *(Fig. 3b)*. T-lymphocytes were also found between the basal cells of the terminal compartments and sebocytes, which is probably relevant to the pathogenesis of the development of sebaceous gland hyperplasia in PCAS.

In the control group, CD3 (+) cells were more frequent than CD20 (+) cells and diffusely distributed in the deep and superficial layers of the dermis (with a density of 6–8 CD3 (+) cells in the field of view at ×400 magnification), but clusters of CD3 (+) no cells were found in the divisions of the pilosebaceous unit. Also, single T-lymphocytes (at the level of 3–4 CD3 (+) cells in the field of view when magnified ×400) were found around blood vessels, sweat glands and among keratinocytes.

Evaluating the distribution and ratio of subpopulations of T-lymphocytes – CD4 (+) and CD8 (+), it is necessary to emphasize their different functions. Namely, $CD4^+$–T-helpers are responsible for activation of B-lymphocytes (humoral immunity), macrophages (cellular immunity) and stimulation of inflammation. Also, CD4 (+) receptors have regulatory T-lymphocytes on their surface, which influence the immune response through the maintenance of immune tolerance and block the functions of other T cells. Meanwhile, $CD8^+$–T-cytotoxic lymphocytes can destroy cells infected with intracellular pathogens and tumor cells.

Comparing the infiltration density of CD4 (+) and CD8 (+) T-lymphocytes, it was found that CD4 (+) cells had a significant advantage *(Fig. 4)*. A large number of CD4 (+) cells were found in the dermal pouch, the outer and inner root epithelial sheath of the hair follicle *(Fig. 4a)*, around the excretory ducts and secretory compartments of the sebaceous glands (quite densely around the hair-raising muscle) *(Fig. 4c)*, in the form of stromal clusters, which included giant cells of the "foreign body" type, as well as in the areas of the epidermal-dermal junction and among keratinocytes. Evaluating the number of CD8 (+) T-lymphocytes in these localizations, we found small infiltrates of $CD8^+$–T-cytotoxic lymphocytes at the level of 15–20 CD3 (+) cells in the field of view at ×400 magnification *(Fig. 4)*.

Thus, infiltrates of CD3 (+) T-lymphocytes, which were detected in PCAS in the scalp, consist almost entirely of $CD4^+$–T-helper / $CD4^+$–T-regulatory cells, which in turn cause the accumulation of CD20 (+) B-lymphocytes (active humoral immunity), CD68 (+) macrophages (formation of giant cells) and support chronic inflammation.

In the control group, CD4 (+) cells were also recorded more often compared to CD8 (+) cells around vessels in the deep and dermis layers (with a density of 2–4 CD4 (+) cells / 0–1 CD8 (+) cells in the field of view at increased ×400), but no CD8 (+) cells were detected in

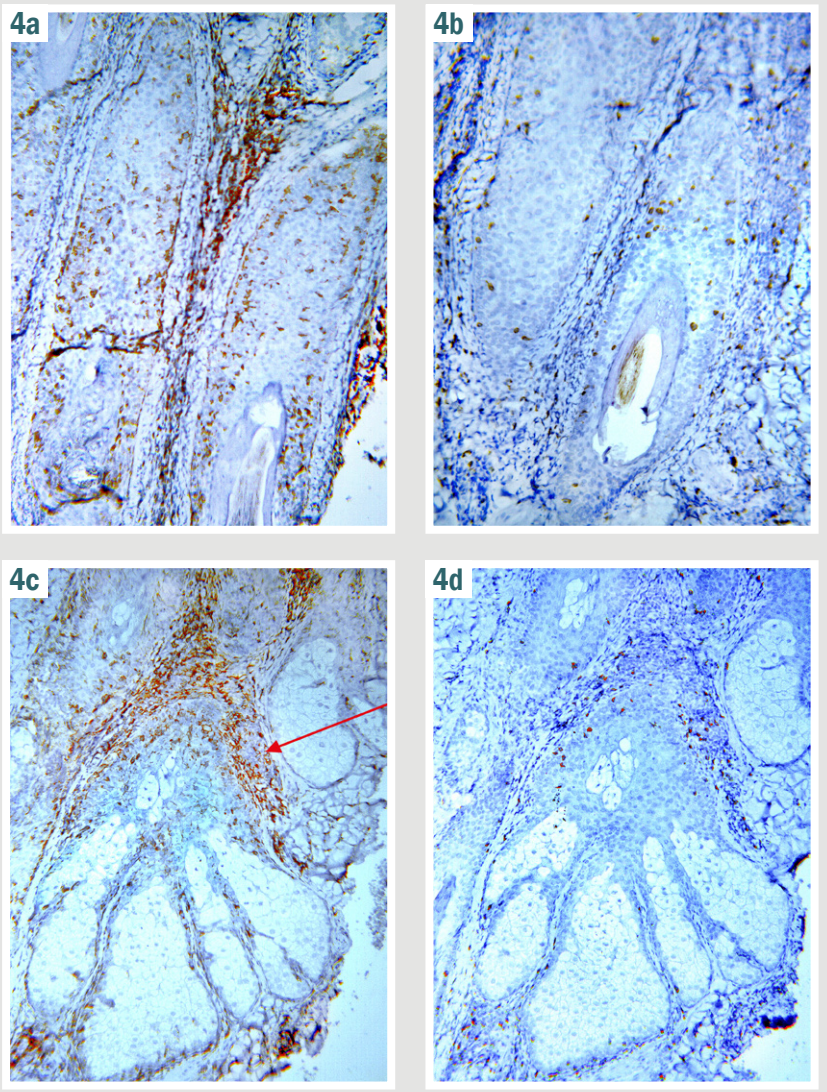

Fig. 4. Layers of deep dermis and subcutaneous tissue of scalp areas, ratio of CD4 / CD8 cells, IHC method with Mayer's hematoxylin (×200). **a:** massive infiltration of CD4 (+) cells of the outer and inner root sheath and stroma of the dermal pouch; **b:** single CD8 (+) cells in the outer root sheath of a hair follicle; **c:** dense infiltration of CD4 (+) cells around the excretory ducts and secretory compartments of the sebaceous glands, which is quite prominent around the elevator pilar muscle (red arrow); **d:** single CD8 (+) cells around the excretory ducts of the sebaceous glands.

the pilosebaceous unit. As a rule, CD4 (+) T-lymphocytes were always found at the border of the epidermal-dermal junction (at the level of 3–4 CD4 (+) cells in the field of view when magnified ×400).

Discussion

According to many researchers, dissecting cellulitis of the scalp or Hoffman's disease, also known as perifolliculitis capitis abscedens et suffodiens, is a severe dermatological disease resulting from occlusion of the follicle due to hyperkeratosis, and possibly has the same mechanism as hidradenitis suppurativa or inverse acne. These dermatoses can be associated with or have an isolated course.

PCAS is one of the primitive cicatricial alopecia of the neutrophilic type (with pustules). The evolution of the disease during the procedures is often with outbreaks and short periods of remission of acne lesions and nodular lesions of the scalp. The characteristic manifestations of PCAS in men that we described during macroscopic examination, such as fluctuating pustules, prominent erythematous nodules on the scalp, pus-filled fistulas, and large patches of alopecia, have been described by all researchers, particularly Qingyun Wu et al. [2]. However, the clinical diagnosis of PCAS is difficult, especially at the initial stage of the disease, so it is very important to collect the correct anamnesis of the disease, a complete clinical examination and the need for paraclinical studies (histopathological study of biopsy of the lesion – microscopy and immunohistochemistry) [3,5,6,7,8].

Immunohistochemical examination in patients with this pathology is very rare in literature, despite its usefulness in understanding the pathogenesis of the disease, which may be due to the reluctance of patients to additionally injure the scalp during punch biopsy or the limitation of diagnostic resources of dermatological clinics. In this aspect, our study is undoubtedly useful, because it contains the results of IHC studies of inflammatory infiltrate cells.

Yuanting Yu et al. in their review, which is also accompanied by a case report of a 15-year-old male patient [1] and Rahul Masson et al. [3], analyzing this problem, emphasize that PCAS is part of the "follicular occlusion tetrad", namely the group of these diseases

includes PCAS, acne conglobata, hidradenitis suppurativa and pilonidal sinus [1]. All of them demonstrate follicular hyperkeratosis, which leads to follicular occlusion with subsequent stretching and rupture of follicles, progressive skin infections with the formation of fistulas and abscesses, which was also thoroughly described in our study.

The etiology of PCAS remains unclear and differs from hidradenitis suppurativa, as evidenced by their varied response to therapy and their histological differences. PCAS involves both follicular dysfunction and an excessive cutaneous immune response to the bacterial flora present, such as staphylococci. In addition, the incidence of PCAS in Ukraine is probably underestimated, due to the lack of referral to specialist dermatologists and the difficult situation due to the war, but this problem is becoming increasingly relevant, especially with the increase in the number of male military personnel over the past eight years.

The literature states that most cases of PCAS can now be effectively treated, however, the lack of clinical studies on PCAS hinders a complete understanding of the disease and limits the ability to define a consensus treatment algorithm [1,2,6,7]. The complexity of treatment and the lack of a single strategy for patients with PCAS are noted by almost all authors, in particular T. Takahashi et al. conducted a review of the current literature in PubMed, Web of Science, Cochrane, and Scopus evaluating new approaches to the treatment of PCAS, and the search provided information on the use of TNF inhibitors after failure of conventional treatments [13].

TNF-α is a cytokine involved in the pathogenesis of inflammatory and autoimmune diseases. Therapeutic drugs act as antagonists by blocking the interaction of TNF-α with type 1 (TNFR1) and type 2 (TNFR2) receptors and have been actively investigated in the last few years, as reported by E. Maxon et al. [7]. However, Rahul Masson et al. together with systemic therapy such as antibiotics and oral retinoids, which are most often used in PCAS, draw attention to procedural treatments such as surgical excision, photodynamic therapy, laser treatment and radiotherapy, which are generally effective in autoimmunization and have a low level of reported side effects [3].

Receptors on the surface of immune cells, which we studied in relation to autoimmunity, divide cells according to the direction of action, such as the humoral link (CD20) and the cellular link (CD3, CD4, CD8) of immunity. Branisteanu D. E. Et al. also describe in their study the distribution of CD20, CD3 and CD8 cells, but do not consider the CD4 subpopulation [6], which, according to our research, has an important antigen-presenting function and significantly exceeds the number of CD8 cells.

To better understand the functional distribution of the cells we studied, it should be noted that the CD20 cluster of differentiation is mainly expressed on B-lymphocytes, a marker that stains 35–37 kDa molecular structures of the tetraspan family (TM4SF), which is related to calcium ion channels and plays a possible role in the activation and regulation of B cells. In turn, the expression of the CD3 differentiation cluster occurs on the surface of T-cells and is responsible for signal transmission to antigen receptors, the molecular weight of which ranges from 20 kDa to 28 kDa, is part of the cytoplasmic tail of the ITAM complex (immunoreceptor tyrosine activating motif) and includes 3 CD3γ subunits, CD3ε, CD3δ [10]. According to D. E. Branisteanu et al., it was CD3 positive cells that occupied up to 90 % of the entire lymphoid infiltrate, and CD20 positive B lymphocytes were single and located around the vessels [6]. These data completely contradict our results, where the density of CD20 positive B-lymphocytes was by no means lower, and sometimes even higher, than CD3 positive T-lymphocytes, and could differ only in localization and depth of location in the dermis. In addition, our work separately investigated the location of the inflammatory infiltrate in the structures of the pilosebaceous unit, which we did not find in any published study.

The protection of the body, which is provided by the effector functions of T-lymphocytes, is called cellular immunity. T-lymphocytes are important for the elimination of microbial pathogens that multiply intracellularly, as well as for the elimination of some extracellular pathogens, most often by recruiting other leukocytes. CD4 has a molecular weight of 55 kDa and belongs to the Ig superfamily, performs the function of a coreceptor during the activation of T cells or macrophages; whereas activation can be induced by any antigen and restricted by the major histocompatibility complex of class II. $CD4^+$–T-helpers can differentiate into four types – Th1 (cytokine IFN-y), Th2 (cytokine IL-4, IL-5, IL-13), Th17 (cytokine IL-17, IL-22), Tfh (cytokine IL-21) responsible for immune responses with activation of macrophages (Th1), activation of eosinophils and mast cells, alternative activation of macrophages (Th2), mobilization and activation of neutrophils (Th17) and production of B-cell antibodies (Tfh) [10]. Our study revealed a significant accumulation of $CD4^+$–T-regulatory cells as an effector link of antigen-presenting cell immunity. Together with the activation of B-lymphocytes, this situation indicates in favor of autoimmunization, which is also noted by Yuanting Yu et al. [1].

CD8 is a heterodimer of two subunits CD8a and CD8b, having a molecular weight of 34 kDa and belonging to the Ig superfamily, which performs the function of a coreceptor during the activation of T-cells or a separate population of dendritic cells; whereas activation can be induced by any antigen and restricted by the main histocompatibility complex of class I [10]. Branisteanu D. E. et al. in their IHC studies of inflammatory infiltrates examined the fraction of $CD8^+$–T-lymphocytes and noted their small proportion among CD3+ lymphocytes [6], which coincides with our results: the majority of CD3+ lymphocytes were identified by us as $CD4^+$–T-helpers.

An increase in the number of $CD4^+$–T-helper and $CD20^+$–B-lymphocytes compared to $CD8^+$–T-cytotoxic lymphocytes in PCAS indicates a powerful humoral response that is responsible for the protection of the host organism through secreted antibodies that are effective in combating extracellular microorganisms and their toxins. It is believed that the humoral response is most powerful against microorganisms that have a capsule of polysaccharides and lipids, which become a target for produced antibodies, while $CD8^+$–T-cytotoxic lymphocytes can respond only to protein antigens. Thus, the study of the features of the immune response in PCAS indirectly helps to clarify the spectrum of etiological factors for improving the treatment strategy.

Conclusions

1. Thus, the pathohistological picture of damage to the pilosebaceous unit of the scalp in PCAS is characterized by a deep inflammatory infiltrate located at the level of the reticular dermis or hypodermis, the development of perifolliculitis in the direction of the formation of deep abscesses and the destruction of polysal follicles with the formation of lymphoplasmacytic granulomas or granulomas with giant cells, ligamentous hyperplasia of the apparatus of sebaceous glands opening into the hair follicle. Given the bactericidal and fungicidal properties of each fat that actively produces sebaceous glands, their hyperplasia in PCAS may be an indirect confirmation of an adaptive response to commensal biological factors in the development of this pathology.

2. Accumulation of CD20 (+) cells in the outer root epithelial sheath and CD3 (+) cells in the outer and inner root epithelial sheath around the shaft of the hair follicle bud, which is a source of stem cells for reparative regeneration of the epidermis and epithelization of the wound surface of the skin, probably leads to a prolonged period of healing and alopecia in PCAS.

3. The high density of infiltration by CD20 (+) and CD3 (+) cells in the excretory ducts of the sebaceous glands and CD3 (+) cells in the secretory departments of the sebaceous glands probably leads to hyperplasia of the sebaceous gland apparatus, as a reactive process of reparative regeneration in PCAS.

4. The predominance of $CD4^+$–T-helpers, compared to $CD8^+$–T-cytotoxic lymphocytes, among the CD3 (+) cells of the inflammatory infiltrate in PCAS indicates the superiority of the effector mechanisms of the immune response, which as a result leads to the activation of macrophages, neutrophils and CD20 (+) B-lymphocytes, which is reflected in the accumulation of these cells in the foci of chronic inflammation around pilosebaceous units of the scalp.

Prospects for further research. Continuing the study of Hoffman's disease requires information on the expression of markers of intercellular adhesion in the epidermis and hair follicles, as well as the state of vascularization around pilosebaceous units, which may be the cause of hair loss due to damage to the reparative properties of stem cells in hair follicles.

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