**Master Thesis**

# DERMATOSCOPIC CRITERIA IN ACNEIFORM RASHES IN ONCOLOGIC PATIENTS: DIAGNOSTIC CRITERIA BASED ON COMPARATIVE CROSS-SECTIONAL STUDY


submitted by

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AUTHOR'S DECLARATION

Unless otherwise indicated in the text or references, or acknowledged above, this thesis is entirely the product of my own scholarly work. Any inaccuracies of fact or faults in reasoning are my own and accordingly I take full responsibility. This thesis has not been submitted either in whole or part, for a degree at this or any other university or institution. This is to certify that the printed version is equivalent to the submitted electronic one.

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ABBREVIATIONS

EGFR - epidermal growth factor receptor

ATP - adenosine triphosphate

KLF4 - Krüppel-like transcription factor 4

TLR2 - toll-like receptor 2

IL - interleukin

TNF-a – tumor necrosis phactor alpha

MEK - mitogen-activated protein kinase kinase

BRAF - B-Raf proto-oncogene

SCC – squamous cell carcinoma

KA – keratoacanthoma

AGEP - Acute generalized exanthematous pustulosis

CTCAE - common terminology criteria for adverse events

GEA scale - Global Evaluation Acne scale

# INTRODUCTION

Modern oncology is characterized by the regular introduction of new antitumor drugs that actively suppress the proliferation of tumor cells through targeted action on pathogenetically significant targets. Success in lowering mortality rates observed in in oncology was largely possible due to the introduction of new targeted antitumor drugs. Their mechanism of action consists of selective action on signaling molecules that play key roles in oncogenesis. The skin, as an actively proliferating organ, expresses many of the targets that antitumor drugs act on. Therefore, it is not surprising that dermatological adverse events of targeted antitumor therapy are among the top three most common adverse events of antitumor therapy.

The spectrum of possible dermatological adverse events developing during antitumor therapy is quite wide, and includes pathological changes of skin and skin appendages. Spectrum of skin changes depends on antitumor drug and it's mechanism of action, and may vary from macular-papular rush, acneiform rush, but one of the most common forms of rash is papulopustular rash developing against the background of therapy with various targeted drugs (primarily EGFR inhibitors - in almost 100% of cases, MEK inhibitors used in monotherapy or in combination with BRAF inhibitors).

Papulopustular rash associated with antineoplastic therapy should be differentiated from true dermatoses presenting with papules and pustules, e.g. acne and other similar drug-induced rashes, such as pustulosis, including acute generalized and acute localized exanthematous pustulosis, which may progress to a life-threatening degree of severity. Differential diagnosis and early diagnosis of this potentially dangerous condition is very important and will allow timely and correct decisions to be made regarding the treatment of dermatological adverse events.

At the same time, patients often receive combined antitumor treatment regimens, and sometimes each of the several drugs taken can cause a rash. Therefore, identifying the true provocateur among the drugs taken is extremely important for the correct correction of the treatment tactics and making a decision on further therapy for the patient.

Patological verification of the diagnosis is most often used in unclear cases, but biopsy as an invasive technique is associated with additional trauma of the patient and potentially influences the health-related life quality. Non-invasive diagnostic methods are especially attractive for early diagnostics of rashes in oncological patients, since their use does not reduce the quality of life of patients. Among such non-invasive methods of diagnosing skin rashes, dermatoscopy is the leader due to its availability and low cost of the study.

At the same time, studies devoted to the study of rashes induced by antitumor therapy are rare, have descriptive design, based on case reports or small case series. Studies available in literature do not assess differential diagnostic criteria in oncologic patients with skin toxic reactions. Only few studies assess the characteristics of rashes during dermatoscopy in ultraviolet light, but theu are devoted to prevalent skin disorders and do not include oncological patients with skin tixic reactions.

Oncologists together with dermatologists supply dermatological supportive therapy of oncological patients and need additinal diagnostic criteria to differetiate acneiform rush at early stages. In patients with acneiform rush caused by targeted therapy acne can be a concomitant or preexisting disorder. Patients receiving chemotherapy, sometimes in combination with targeted therapy are at risk of developing exanthematous pustulosis which can at early stages have similar presentation to early acneiform ruch. And timely detection of exanthematous pustulosis can contribute to proper  treatment of this potentially life treatening disorder. Dermatoscopy as a non-invasive diagnostic tool has a substantial advantage in this

category of patients because this examination does not negatively influence the health related life quality.

Therefore, the study of differential diagnostic criteria of papulopustular dermatoses developing against the background of antitumor therapy using non-invasive techniques such as dermatoscopy is of particular value in dermato-oncological practice.

# LITERATURE REVIEW

## 1. Skin toxic reactions and acneiform rash during therapy with EGFR inhibitors

When prescribing drugs from the group of monoclonal antibodies to epidermal growth factor receptor (EGFR) AEs in the form of acneiform rashes develop in 50-90% of cases. Drugs of this class currently play an important role in the treatment of patients withcolorectal cancer (cetuximab and panitumumab), head and neck tumors (cetuximab), lung cancer (gefitinib, erlotinib and afatinib), pancreatic cancer (erlotinib), breast cancer (lapatinib). It has been proven that acneiform rash significantly reduces the quality of life of patients, causing significant emotional and physical discomfort. Low efficiency of acneiform rash treatment reduces patient compliance with the treatment, often leads to a change in the antitumor therapy regimen or its complete cancellation, which certainly affects the treatment results and patient survival rates. It is important to note that a direct correlation has been proven between the severity of acneiform rash and the therapeutic effect of EGFR inhibitors: skin reactions serve as a kind of marker of effectiveness.

An important mechanism in the cell signaling pathway is protein phosphorylation, which occurs via protein kinases [1]. This mechanism regulates fundamental processes of cell proliferation and differentiation.

The most important protein kinases are serine/threonine and tyrosine kinases, which are characterized by the ability to catalyze the phosphorylation of serine/threonine or tyrosine amino acid residues in proteins, respectively. There are two classes of tyrosine kinases: receptor tyrosine kinases and cellular tyrosine kinases. Receptor tyrosine kinases consist of an extracellular ligand binding domain, a transmembrane domain, and an intracellular catalytic domain. Dimerization of two receptor tyrosine kinases upon ligand binding leads to autophosphorylation of tyrosine residues in the intracellular catalytic domains, which leads to an active conformation and subsequent activation of the signal transduction cascade inside the

cell. In this downstream signal cascade, cellular tyrosine kinases play a major role. The latter are located in the cytoplasm or in the cell nucleus.

Figure 1 shows an example of signal transduction pathways via protein phosphorylation of EGFR.Homodimerization or heterodimerization of two epidermal growth factor receptors activates a tyrosine kinase phosphorylation cascade, resulting in increased proliferation and decreased apoptosis.

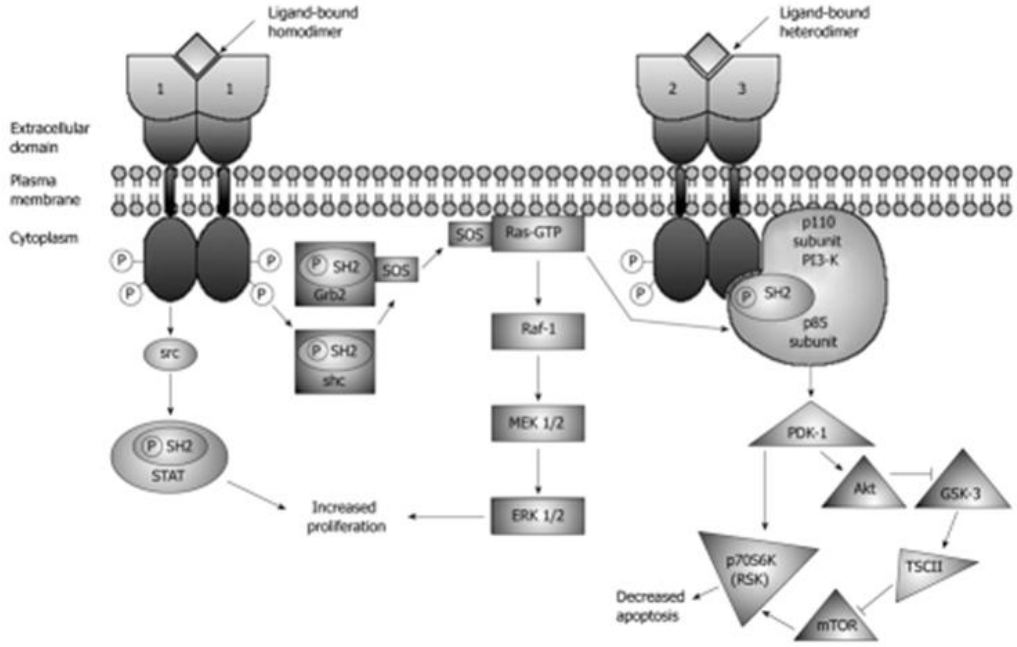



**Fig. 1. Activation of the signaling pathway involving tyrosine kinases [1]**

Due to their significant impact on cells, tyrosine kinases have a complex regulatory system. When tyrosine kinases become activated and no longer dependent on ligands due to mutations or overexpression, unregulated cell proliferation occurs, leading to tumor development. For this reason, tyrosine kinase inhibitors can serve as anticancer agents, by influencing which this unregulated process can be hindered.

Epidermal growth factor receptor EGFR (or HER1) is a transmembrane glycoprotein (170 kD) that belongs to the epidermal growth factor receptor family. The EGFR family

consists of the EGFR tyrosine kinase receptors (ErbB1, Her1), ErbB2 (Her2), ErbB3 (Her3), and ErbB4 (Her4). EGFR is involved in the regulation of cell proliferation and differentiation processes, and is expressed on the surface of both normal and transformed epithelial cells. It has a structure typical of all receptor tyrosine kinases and consists of three fragments: the ligand-binding part is represented by the extracellular domain, the transmembrane part is the hydrophobic region, and the intracellular fragment is the tyrosine kinase domain (Fig. 2).

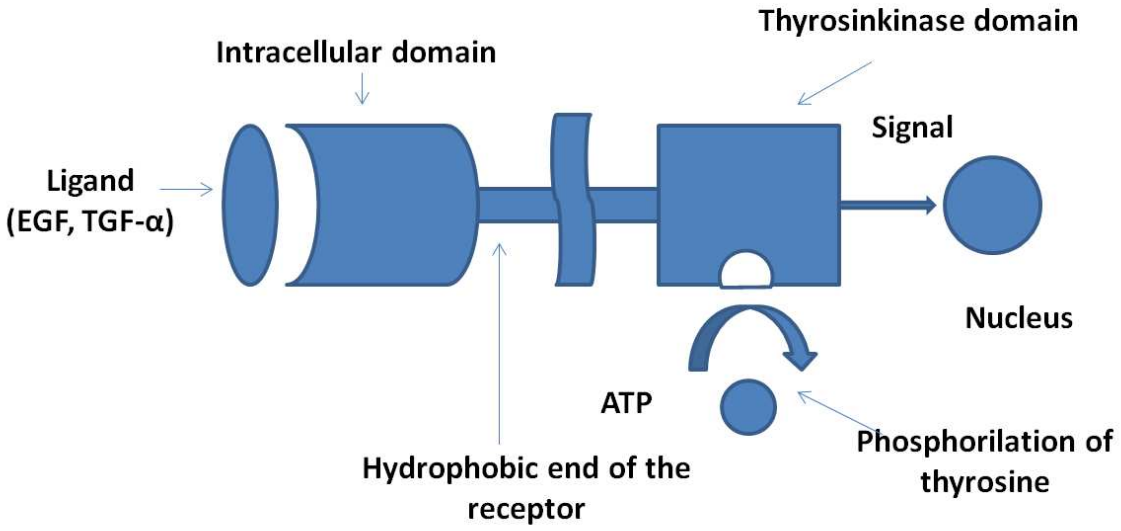



**Fig. 2. Schematic structure of the epidermal growth factor receptor (EGFR)**

Skin toxic reactions of EGFR inhibitors are divided into three categories depending on their clinical manifestation: damage to the sebaceous hair follicle (associated with EGFR inhibitors folliculitis - acneiform rash, which occurs early in the course of treatment; changes in the skin barrier, primarily manifested by xerosis, cracks and itching, often occur late; lesions of the skin appendages (paronychia), purulent granuloma, hair changes, which occur less frequently.

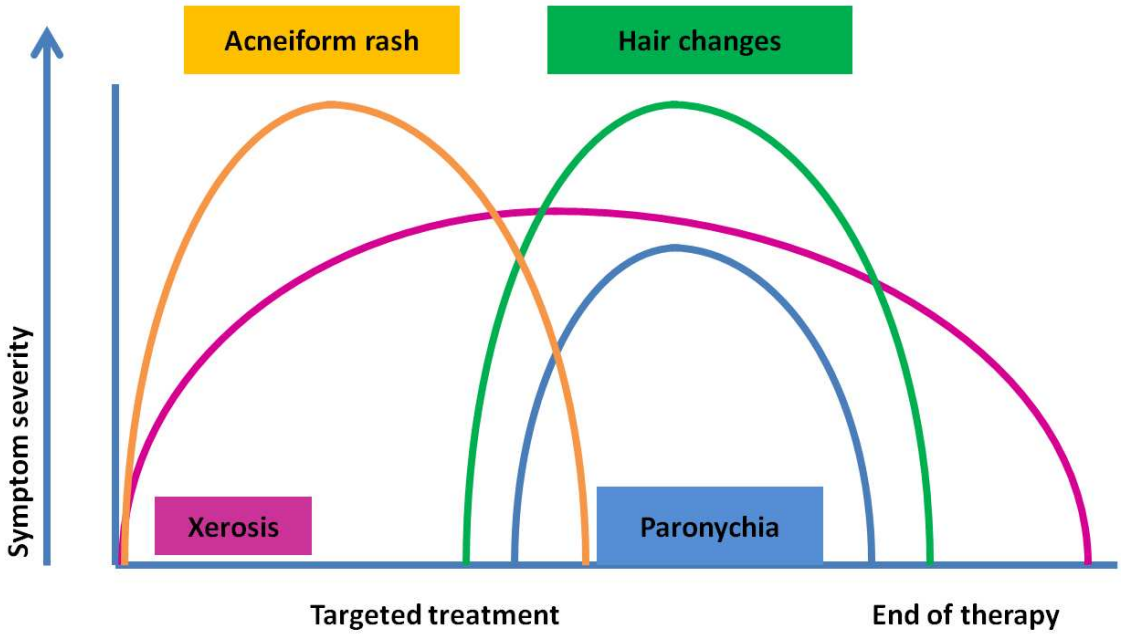



**Fig. 3. Spectrum and timing of development of dermatological toxicity of EGFR inhibitors**

Skin toxic reactions occur in 80% of cases in patients and are the most common adverse events when using this group of drugs. Even if the severity of the side effect does not reach 3-4 degrees (about 20%), toxic reactions with skin manifestations significantly reduce the quality of life of patients. Thus, skin toxicity negatively affects the ability to carry out full course of antitumor therapy, which is confirmed by the results of a survey of patients undergoing therapy.

**Pathogenesis of acneiform rash in the context of targeted antitumor therapy**

During iEGFR and iMEK treatment, Krüppel-like transcription factor 4 (KLF4) accumulates and binds the IL-36γ promoter together with the transcription factor kappa beta (NF-κB) activated by P. acnes via toll-like receptor 2 (TLR2) and stimulates IL-36γ expression.

IL-36γ induces the expression of IL-8, which attracts neutrophils into the follicle. This

contributes to the formation of folliculocentric pustular drug eruption [2].

The pathogenesis of skin rashes is based on the mechanism of inhibition of EGFR expression in keratocytes of the Malpighi germ layer, papillae of hair follicles and sebaceous glands, which initiates an increase in the synthesis of cytokines such as IL-1 and TNF-a and the development of aseptic inflammation. Due to the inhibition of the synthesis of antimicrobial peptides by EGFR inhibitors, various representatives of the microflora of integumentary tissues are activated, including Staphylococcus aureus, which leads to the transformation of aseptic inflammation into infectious inflammation. There is conflicting information regarding the duration of the development of this process. Thus, Amitay-Laish I. indicates a duration of up to several months, while Sanmartin O. defines this stage as 2-3 weeks [3,4]. According to Osio A., in one third of patients, peeling can become significant, the scales become thick, yellow and greasy, which creates conditions for the addition of a secondary bacterial infection [5.]. During pathomorphological examination in the area of the follicles, superficial perifolliculitis with an inflammatory infiltrate around the enlarged and filled with horny masses follicle mouth, as well as neutrophilic suppurative folliculitis are determined Also, pronounced changes in the pilosebaceous structures are noted in the form of a decrease in their size, insufficient differentiation of sebocytes and keratinocytes, and an infiltrate of inflammatory cells. The stratum corneum becomes thinner, loses its structure like a “brick wall”, and along with the phenomena of epidermal atrophy, dyskeratosis and impaired maturation of keratinocytes of varying severity occur [6,7,8].

Among patients receiving EGFR inhibitors almost 90% developed skin toxicity, among them dose reduction was needed in 60% due to cutaneous side effects of EGFR inhibitors, treatment discontinuation in 32% and interruption of treatment was recommended in 76% of cases [9].

## 2. Skin toxic reactions and acneiform rash during therapy with BRAF and MEK inhibitors

The use of BRAF inhibitors in monotherapy is associated with compensatory hyperactivation of signaling involving MEK, which activates cell proliferation, which is associated with an increased frequency of skin changes associated with increased proliferation and keratinization. Therefore, the use of combined targeted therapy (BRAF inhibitor + MEK inhibitor) is preferable. It has been proven that combined targeted therapy of melanoma allows not only to reduce the incidence of dermatological adverse events (Table 1) (with an increase in the incidence of tolerated adverse events from the gastrointestinal tract), but also to increase overall and relapse-free survival of patients.

Table 1. Incidence of dermatological adverse events with BRAF inhibitor therapy compared with combination therapy with BRAF and MEK inhibitors (10)

| Adverse event | Dabrafenib + trametinib (n=209) | | Dabrafenib (n=211) | |
|---|---|---|---|---|
| | Any degree | 3rd degree | Any degree | 3rd degree |
| Any undesirable phenomenon | 199 (95) | 66 (32) | 203 (96) | 72 (34) |
| Rash | 48 (23) | 0 | 46 (22) | 2 (1) |
| Peripheral edema | 30 (14) | 1 (<1) | 10 (5) | 1 (<1) |

| | | | | |
|---|---|---|---|---|
| Xerosis | 19 (9) | 0 | 28 (13) | 0 |
| Itching | 17 (8) | 0 | 26 (12) | 0 |
| Alopecia | 15 (7) | 0 | 55 (26) | 0 |
| Palmar-plantar syndrome | 10 (5) | 0 | 58 (27) | 1 (<1) |
| Hyperkeratosis | 7 (3) | 0 | 68 (32) | 1 (<1) |
| Skin papilloma | 3 (1) | 0 | 45 (21) | 0 |
| Squamous cell carcinoma including keratoacanthoma | 5 (2) | 4 (2) | 20 (9) | 8 (4) |
| Acneiform rash | 16 (8) | 0 | 7 (3) | 0 |

A systematic review of prospective phase I, II, and III studies and expanded access programs in patients with melanoma receiving dabrafenib monotherapy (150 mg, twice daily) or combination therapy with dabrafenib (150 mg, twice daily) plus trametinib (2 mg, once daily) assessed the incidence and risk of all-grade skin toxicity. The pooled hazard ratio (HR) showed that the combination of dabrafenib with trametinib compared with dabrafenib alone was associated with a significantly increased risk of all-grade rash (HR 1.35, 95% CI 1.01 to 1.80) and a reduced risk of squamous cell carcinoma (HR 0.40, 95% CI 0.18 to 0.89), alopecia (HR 0.19, 95% CI 0.12 to 0.30), and hyperkeratosis (HR 0.25, 95% CI 0.10 to 0.62) [10].

Thus, after a period of active research, three combinations of BRAF and MEK inhibitors have entered widespread practice: dabrafenib + trametinib (dabra+tram), vemurafenib + cobimetinib (vem+cobi),encorafenib + binimetinib (enco+bini). In Russia, the first two pairs of drugs were included in clinical guidelines for the treatment of melanoma at the moment oft he study.

Manifestations of skin toxicity in the structure of adverse events of combination therapy with BRAF and MEK inhibitors occupy one of the leading positions in terms of frequency of development (Fig. 2), while the spectrum of clinical changes in the skin and its appendages is quite wide.

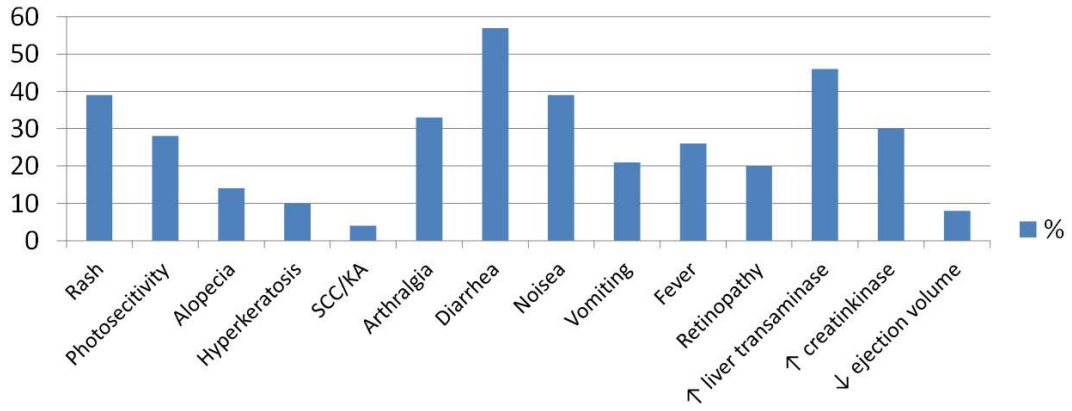



*Fig. 2. The structure of adverse events during combination therapy with vemurafenib and cobimetinib. (SCC – squamous cell carcinoma; KA – keratoacanthoma)(11)*

Thus, according to L.Heinzerling and co-authors, the most common manifestations of skin toxicity of combination therapy with BRAF and MEK inhibitors are rash, including maculopapular rash, increased sensitivity to ultraviolet (UV) radiation, hair loss, various

keratinization disorders and the formation of new primary skin neoplasms, both benign and malignant (Table 2) [11]. In some cases, the severity of the skin process can reach grade 3 or 4 and cause a forced interruption in treatment, a reduction in the dosage of drugs, or even complete cancellation of therapy and transfer of the patient to other possible treatment methods [12 ]. It has been proven that the incidence of adverse events with combination therapy is lower than with vemurafenib monotherapy, so the combination with cobimetinib is increasingly entering practice [10].

Table 2. Structure of adverse dermatological events during combination therapy with vemurafenib and cobimetinib,abs. (%) [11]

| **Manifestation of skin toxicity** | **All degrees of severity** | **3 and 4 degrees of severity** |
|---|---|---|
| **Rash** | | |
| Rash | 101 (40.9) | 13 (5.3) |
| Rash maculopapular | 38 (15.4) | 18 (7.3) |
| Acneiform dermatitis | 34 (13.8) | 6 (2.4) |
| Erythema | 26 (10.5) | 0 |
| Itching | 49 (19.8) | 3 (1.2) |
| Dry skin | 38 (15.4) | 2 (0.8) |

| | | |
|---|---|---|
| **Manifestations of increased sensitivity to UV** | | |
| Photosensitization | 84 (34.0) | 1 (0.4) |
| Sunburn | 37 (15.0) | 2 (0.8) |
| **Pathology of the skin appendages** | | |
| Alopecia | 41 (16.6) | 1 (0.4) |
| **Keratinization disorders** | | |
| Hyperkeratosis | 25 (10.1) | 1 (0.4) |
| Palmoplantar keratoderma | 5 (2.0) | 0 |
| Palmar-plantar erythrodysesthesia | 17 (6.9) | 0 |
| Follicular keratosis | 9 (3.6) | 0 |
| **Skin neoplasms** | | |
| Skin papilloma | 17 (6.9) | 0 |
| Basalioma | 15 (6.1) | 14 (5.7) |
| Actinic keratosis | 13 (5.3) | 8 (3.2) |
| Squamous cell skin cancer | 10 (4.0) | 9 (3.6) |
| Keratoacanthoma | 4 (1.6) | 3 (1.2) |

Some studies also compared the spectrum and frequency of toxic reactions in patients receiving different types of combination targeted therapy (Table 3).

Table 3. Spectrum and frequency of development of skin toxic reactions during targeted therapy of melanoma with various combinations of drugs [11]

| **Combination of braf and mek inhibitor** | **Dabrafenib + trametinib** | | **Vemurafenib + cobimetinib** | | **Encorafenib + binimetinib** | |
|---|---|---|---|---|---|---|
| **Study** | COMBI-V | | coBRIM | | COLUMBUS Part 1 | |
| **Duration of observation (months)** | 19.8 months | | 18.5 | | 16.6 | |
| **Number of patients (safety assessment sample)** | 352 (350) | | 247 (247) | | 192 (192) | |
| **Adverse event severity (CTC AE scale)** | **Any** | **3-4** | **Any** | **3-4** | **Any** | **3-4** |
| **Rash*** | 84 (24.0) | 3 (0.9) | 101 (40.9) | **13**(5.3) | 27 (14.1) | **2**(1,0) |
| **The rash is maculopapular)** | 13 (3.7) | 2 (0.6) | 38 (15.4) | **18**(7.3) | 3 (1.6) | 0 |
| **Dry skin** | 33 (9.4) | 0 | 38 (15.4) | 2 (0.8) | 27 (14.1) | 0 |
| **Itching** | 36 (10.3) | 0 | 49 (19.8) | 3 (1,2) | 21 (10.9) | **1**(0.5) |
| **Erythema** | 35 (10.0) | 0 | 26 (10.5) | 0 | 13 (6.8) | 0 |
| **Acneiform dermatitis*** | 23 (6.6) | 0 | 34 (13.8) | 6 (2.4) | 6 (3.1) | 0 |
| **Alopecia** | 23 (6.6) | 0 | 41 (16.6) | 1 (0.4) | 26 (13.5) | 0 |
| **Hyperkeratosis** | 18 (5.1) | 0 | 25 (10.1) | 1 (0.4) | 27 (14.1) | 1 (0.5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Palmoplantar keratoderma** | - | - | 5 (2.0) | 0 | 17 (8.9) | 0 |
| **Palmar-plantar erythrodysesthesia*†** | 14 (4.0) | 0 | 17 (6.9) | 0 | 13 (6.8) | (0) |
| **Actinic keratosis** | 5 (1.4) | 0 | 13 (5.3) | 8 (3.2) | - | - |
| **Pityriasis versicolor (keratosis pilaris)*** | 4 (1.1) | 0 | 9 (3.6) | 0 | 9 (4.7) | 0 |
| **Photosensitivity reactions*** | 15 (4.3) | 0 | 84 (34.0) | 1 (0.4) | 8 (4.2) | 1 (0.5) |
| **Sunburn** | 3 (0.9) | 0 | 37 (15.0) | 2 (0.8) | 0 | 0 |
| **Squamous cell skin cancer*** | 5 (1.4) | **5**(1,4) | 10 (4.0) | 9 (3.6) | 5 (2.6) | 0 |
| **Keratoacanthoma*** | 2 (0.6) | 2 (0.6) | 4 (1.6) | 3 (1,2) | 4 (2.1) | 0 |
| **Papilloma*** | 8 (2.3) | 0 | 17 (6.9) | 0 | 12 (6.3) | 0 |
| **Basal cell carcinoma*** | 3 (0.9) | 2 (0.6) | 15 (6.1) | 14 (5.7) | 3 (1.6) | 0 |

At the same time, it is important to emphasize that the development of maculopapular rash is more associated with treatment with BRAF inhibitors, and the appearance of acneform rash is much more associated with treatment with MEK inhibitors. Thus, according toAccording to R. Anforth et al., skin toxicity in the form of papulopustular rashes is more typical for mek inhibitors and is observed in 77% of patients with monotherapy with drugs from this group [13]. This can be taken into account when deciding to reduce the dose of drugs (i.e., perhaps, with the development of acneiform rash, it is advisable to begin changing the dosage of antitumor drugs with an isolated reduction in the dose of the MEK inhibitor).

The clinical and dermatoscopic characteristics of the rash are similar to acneiform eruptions that develop during therapy with epidermal growth factor receptor inhibitors. As a rule, the papulopustular rash occurs primarily on the skin of the face, and as the severity

increases, similar elements appear on the skin in areas rich in sebaceous glands (skin of the chest, upper third of the back), as well as on the skin of other areas of the trunk and proximal parts of the extremities. The rash usually differs from acne vulgaris by the absence of comedones, although comedones have been described during therapy with vemurafenib. Papules and pustules are located on an erythematous base and quickly become covered with crusts. The median time of rash onset is 12.5 days with monotherapy with mek inhibitors, and 307 days with combination therapy. Dermatoscopically, according to our observatioins, the rash reveals similarities with acneiform eruptions caused by EGFR inhibitors, characterized by the formation of pustules in the form of white rounded zones, in the center of which a yellow lump is determined, histologically corresponding to a follicular hyperkeratotic plug. Pathomorphological examination may reveal pustules formed by a neutrophilic perifollicular infiltrate, ruptured follicles.

### 3. Acute exanthematous pustulosis against the background of antitumor therapy

There are acute generalized and acute localized exanthematous pustulosis depending on the extent of the skin lesion. Acute generalized exanthematous pustulosis (AGEP) is a rare form of severe reaction, occurring with skin lesions and possible addition of systemic symptoms. AGEP is usually provoked by taking medications, but infectious agents can also serve as a provoking factor.

The onset of the disease is characterized by the rapid appearance and spread of multiple sterile pustules, including those prone to merging, which are located against a background of bright red homogeneous erythema with unclear borders. A threat to life in AGEP may be associated with damage to the liver, kidneys, the development of sepsis or multiple organ damage.

The AGEP was first described in 1968, when Baker H. and Ryan TJ published a study of 104 cases of generalized pustular psoriasis with similar clinical symptoms [14]. And the term "acute generalized exanthematous pustulosis" was actually proposed in 1980 by Beylot C., Bioulac P. and Doutre M.S. to describe cases of pustular eruptions that quickly arise against the background of taking medications.

Further studies of AGEP and other life-threatening conditions such as Lyell's syndrome, Stevens-Johnson syndrome, and DRESS syndrome have led to the current understanding of AGEP as a rare but severe skin reaction to medications that, due to the potential for life-threatening complications, requires immediate medical attention and close monitoring of the patient's condition.

The underlying mechanism of AGEP is delayed-type hypersensitivity (type IV) to drugs. T cells play a key role in this process, mediating the inflammatory response. Upon initial exposure to a drug, the immune system becomes sensitized, and upon repeated exposure, activated T cells recognize the antigen and initiate an inflammatory cascade. This leads to the release of cytokines such as interleukin-8 (IL-8), which attracts neutrophils to the site of inflammation, promoting pustule formation.

Clinically, AGEP is characterized by the sudden appearance of numerous small sterile pustules on an erythematous background. These pustules are often grouped and may coalesce to form larger pustular areas. Typical locations of the rash include the flexor surfaces of the extremities, trunk, and face, but the rash may spread over the entire body. Itching is common. Mucosal involvement is rare, but when it occurs, the location is limited to the lips or buccal mucosa. Such skin manifestations usually occur 24-48 hours after taking the drug [15].

One of the characteristic signs of AGEP is fever, which usually appears 1 day after the appearance of the rash, and the average duration is 2 days.

Patients may also complain of chills, general malaise and muscle pain.

Skin changes in AGEP usually regress within 2 weeks after the cessation of the provoking drug, but in severe cases pustules may persist for a longer period.

There are few papers repotring dermatoscopic picture in acute generalized pustulisis which describe milky globules on monomorphoud erythematous background [16].

## 4. Clinical characteristics of acne

Acne is a common inflammatory disease of the sebaceous hair follicles. The clinical picture is characterized by the formation of comedones (open and/or closed), papules, pustules, and nodes. Most often, the rashes are located on the skin of the face, chest, and back.

A wide range of factors are involved in the pathogenesis of acne including use of several medications, genetic factors, endocrine disorders, insulin resistance, use of occlusive wear, repetitive mechanical trauma and others [17].

Acne rashes may exist before the start of antitumor therapy, especially in young patients, and may mimic acneiform rashes in the initial stages. In turn, acute exanthematous pustulosis, althow presents with peculiar morphology of skin lesios also requires differential diagnosis with acneiform rashes during antitumor therapy, since early correct diagnosis can facilitate early administration of appropriate therapy and prevent the progression of this disease to a life-threatening degree of severity.

## 5. Dermatoscopic diagnostics of acne, acute exanthematous pustulosis and acneiform rashes during antitumor therapy: the state of the problem

There are few publications devodet to dermatoscopic assessment of acneiform rush caused by targeted antitumor therapy, acute exanthematous pustulosis and acne.

Dermatoscopic signs of skin toxicity of anti-tumor therapy was assessed in a study of

rashes caused by vemurafenib [18]. Rajczykowski M. and colleagues describe wide variety of skin toxicities they observed in patients receiving vemuragenib. Aneiform rush in this study was not characterized in detail, only comedones and intrafollicular yellowish plugs, surrounded by multiple, wellvisible erythralgic telangiectasia are mentioned as dermatoscopic sighns of acneiform rush. No studies assessed acneiform rush caused by targeted antitumor therapy in ultravioled dermatoscopy.

Dermatoscopic sighns of acute exanthematous pustulosis is described in few studies. Errichetti E. and colleagues describe a case of acute generalized exanthematous pustilosis caused by spider bite [18, 19]. Authors describe the rush in detail as small, creamy white, roundish globules corresponding to non-follocular pustules, some globules with central brown to black dot corresponding to protruding follicle, partly accompanied by yellow crusts and orange globules (due to spongiosis). No studies assessed papulopustular rush caused by targeted antitumor therapy in ultravioled dermatoscopy.

Dermatoscopic signs of acne were mentioned in only few studies. Markowitz O and colleagues mentioned acne excoriee in comparison to early stage cystic keratoacanthoma and nodular basal cell carcinoma [20]. Authors underline that a localized yellow hue in acne excoriee can mimic small erosions seen in basal cell carcinoma. Errichetti E and colleagues were the first who described also dermatoscopic signs of acne in ultraviolet dermoscopy [21, 22]. They showed that acne lesions were associated with interruption of uniform follicular red fluorescence.

In dermatological supportive therapy of oncological patients it is important to have additinal diagnostic criteria to differetiate acneiform rush caused by targeted therapy from acne which can be a concomitant disorder, and from exanthematous pustulosis which can at early stages have similar presentation to early acneiform ruch. Early detection of exanthematous pustulosis can contribute to timely treatment of this potentially life treatening

disorder. Dermatoscopy has a substantial advantage as a non-invasive diagnostic tool in this category of patients because this examination does not negatively influence the health related life quality.

Therefore, the aim of this study was to assess the dermatoscopic features specific to acneiform rashes associated with antitumor therapy in comparison to acne vulgaris and acute exanthematous pustulosis.

## Methods

### Study design

The design chosen was a multicenter cross-sectional observational continuous study, which allows us to study a representative sample and obtain data on the clinical and dermatoscopic features of acneiform skin toxic reaction against the background of antitumor therapy, acne vulgaris, and pustulosis against the background of antitumor therapy.

### Eligibility Criteria

The inclusion criteria for the study were: age over 18 years, verification of the skin disease (acneiform skin toxic reaction due to antitumor therapy, acne vulgaris, pustulosis against the background of antitumor therapy) by a dermatologist based on the clinical, dermatoscopic picture, according to indications - using a pathomorphological study. The exclusion criteria were age under 18 years, the presence of severe mental disorders, the inability to fill out the questionnaire proposed as part of the study. The exclusion criterion was the patient's refusal of pathomorphological verification of the diagnosis in the presence of clinical and / or dermatoscopic indications for biopsy.

### Conditions of the study

Patients were recruited at the clinical sites of the Department of Dermatovenereology and Cosmetology of the Federal State Budgetary Educational Institution of Higher Professional Education “Central State Medical Academy”: Medical Scientific and Educational Institute of Moscow State University named after M.V. Lomonosov, Institute of Plastic Surgery and Cosmetology, International Institute of Psychosomatic Health.

### Duration of the study

The study was conducted from February 2025 to May 2025.

A special individual registration card was created for patients.

The individual registration card included a questionnaire containing information about the patient: age, gender, education, marital status, professional activity, weight, height.

A separate section was devoted to the study of clinical and dermatoscopic signs of the above skin diseases. Dermatoscopic images were recorded using a Dermlite 5 dermatoscope with an immersion medium (alcohol spray). Each patient had a rash area and areas of apparently unaffected skin between the lesions recorded.

**Methods of recording outcomes**

To register the main and additional outcomes (end points), a specially developed individual registration card (IRC) of patients was used. The first module of the IRC included socio-demografic section (age, gender). The second part included a section for registering the diagnosis, severity of the disease, dermatoscopic signs.

A separate block of the IRC was designed to study pruritus. Pruritus was assessed using several patient-reported endpoints, which were recorded using separate questions or by using validated pruritus scales.

**Primary outcome of the study**

Clinical characteristics included clinical diagnosis, severity grade (CTCAE for acneiform rash, GEA scale for acne; patients with pustulosis had similar disease severity, so due to the lack of a generally accepted scale for assessing this condition, their severity was not analyzed) and disease form.

To describe dermatoscopic signs, two dermatoscopy techniques were used: polarized light and ultraviolet light. Photographs were taken at x10 magnification, and alcohol antiseptic spray was used as an immersion fluid.

**Ethical review**

The study was approved by the local ethics committee of Federal State Budgetary Educational Institution of Additional Professional Education “Central State Medical

Academy" (protocol of the meeting of the local ethics committee № 01/2021 dated 04.02.2021).

**Statistical analysis**

*Principles for calculating sample size:* The sample size was not pre-calculated. All concecutive patients were included due to rarity of acute exanthematous pustulosis.

*Methods of statistical data analysis***:** Statistical data processing was performed using the SPSS 27 program. Qualitative features are presented as absolute and relative frequencies expressed as percentages with the Pearson $\chi 2$ criterion calculated for them. The normality of distribution was tested using the Kolmogorov-Smirnov criterion. Considering the fact that the distribution of parameters in some study groups differed from normal, nonparametric criteria were used to determine the statistical significance of differences. Comparison of quantitative variables was performed using the nonparametric Mann-Whitney U-test or the Kruskal-Wallis test when comparing two or more groups, respectively. The Pearson chi-square test ($\chi 2$) was used to compare the frequencies of categorical features. Statistical data processing was performed using the SPSS Statistics27 program. Differences were considered statistically significant at $p < 0.05$.

## Results

The study involved 74 patients, including 40 (53.3%) men, average age 46.78 years [±19.207 years], including patients with acne, acneiform rashes against the background of antitumor targeted therapy, acute exanthematous pustulosis (Table 4).

Clinical and dermatoscopic images were obtained from patients with acne (n=238), acneiform rashes associated with targeted therapy (n=775), and acute localized exanthematous pustulosis (n=78).

A comparison of patients in the examined groups was conducted. significant differences in age ($p<0.001$) were revealed (Fig. 4).

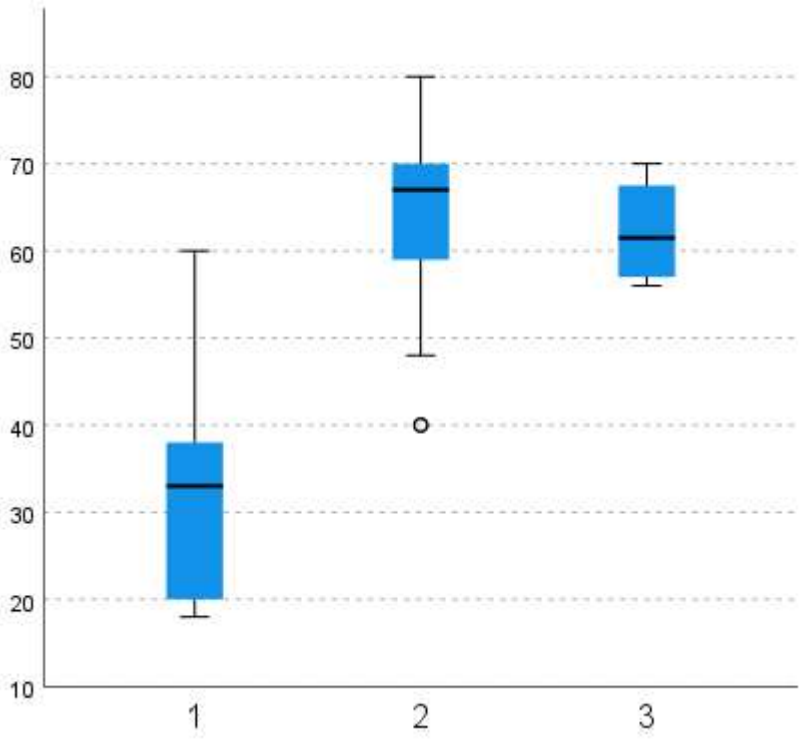



Fig. 4. Age distribution of examined patients.

According to the severity, patients with acneiform rash were distributed as follows: 1 grade was registered in 4 patients (13.4%), 2 grade in 11 (37,9%), and 3 grade in 14 (48,3%).

Among patients with acne, the most common were those with grade 1 skin lesions (n=17, 22.7%), grade 2 – 4 patients (5.3%), grade 3 – 9 (12%), grade 4 – 6 (8%), grade 5 – 1 (1.3%).

Patients with pustulosis received therapy with docetaxel (n=5) or paclitaxel (n=2), or combination therapy with docetaxel, trastuzumab, pertuzumab (n=1).

Patients with acneiform rash were treated with an EGFR inhibitor (n=20) or a MEK inhibitor (n=9).

Table 4. Characteristics of the examined patients

| **Parameter** | **Acne** | **Acneiform rash** | **Pustulosis** | **Significance of differences (chi-square test)** |
|---|---|---|---|---|
| **Number of patients, n (%)** | 37 (50) | 29 (39.2) | 8 (10.8) | - |
| **Male (n (%))** | 20 (54) | 20 (69) | 0 | p=0.002 |
| **Female** | 17 (46) | 9 (31) | 8 (100) | |
| **Age** | 30.76 (27.19-34.34) | 62.83 (58.53-67.12) | 62.25 (57.26-67.24) | p<0.001 |

Table 5. Dermatoscopic signs, detected in each group in polarized regimen

| **Dermatoscopic** | **Acne,** | **Acneiform** | **Pustulosis,** | **Significance of differences (chi-** | **Ref.** |
|---|---|---|---|---|---|

| **parameter** | n (%) | **rash,** n (%) | n (%) | **square test)** | |
|---|---|---|---|---|---|
| **Follicular signes** | | | | | |
| **Yellow clods on skin color area (open comedones)** | 20 (52.6) | 0 | 2 (25) | p<0.001 | Fig. 5 |
| **White-yellow structureless zones with thin red branching vessels** | 26 (68.4) | 4 (13.8) | 2 (25) | p<0.001 | Fig. 6 |
| **Yellow clods (horny plug) surrounded by structureless pink area (erythema)** | 6 (15.8) | 19 (65.5) | 3 (37.5) | p<0.001 | Fig. 7 |
| **White clod with centered yellow clod (keratin plug in the center of the pustule)** | 11 (28.9) | 18 (62.1) | 0 | p<0.001 | Fig.8 |
| **Yellow thick lines protruding from follicles (keratosis follicularis)** | 0 | 16 (55.2) | 0 | p<0.001 | Fig. 9 |

| | | | | | |
|---|---|---|---|---|---|
| **Purple structureless area (haemorrhagic spots)** | 0 | 17 (586) | 0 | p<0.001 | Fig. 10 |
| **Wgite clod (pustule) surrounded by purple area** | 0 | 13 (44.8) | 3 (37.5) | p=0.02 | Fig. 11 |
| **Interfollicular skin** | | | | | |
| **Pink srtuctureless zone (postinflammatory erythema)** | 29 (76.3) | 2 (6.9) | 0 | p<0.001 | Fig. 5 |
| **White clods (pustules) surrounded by structureless red zone (erythema)** | 30 (78.9) | 11 (37.9) | 6 (75) | p<0.001 | Fig. 12 |
| **Structureless red-brown areas (excoriations)** | 12 (31.6) | 0 | 4 (50) | p=0.02 | Fig. 13 |
| **White structureless zones (scarring)** | 12 (31.6) | 0 | 0 | p<0.001 | Fig. 14 |
| **Thin linear vessels on red background** | 0 | 20 (69) | 0 | p=0.02 | Fig. 15 |

| | | | | | |
|---|---|---|---|---|---|
| **(erythema with teleangiectasia)** | | | | | |
| **Purpuric structureless areas** | 2 (5.3) | 6 (20.7) | 1 (12.5) | p=0.001 | Fig. 16 |
| **White clods (pustules) surrounded by thin linear vessels on red background (erythema with teleangiectasia)** | 0 | 23 (79.3) | 4 (50) | p<0.001 | Fig.17 |
| **White clods (pustules) agminated on diffuse erythema** | 0 | 14 (48.3) | 6 (75) | p<0.001 | Fig. 18 |
| **White clods tend to merge** | 0 | 0 | 6 (75) | p<0.001 | Fig. 19 |
| **Crusts** | | | | | |
| **Haemorrhagic crusts** | 2 (5.3) | 10 (34.5) | 0 | p=0.108 | Fig. 20 |
| **Yellow crusts (pyogenic crusts)** | 0 | 8 (27.6) | 0 | p<0.001 | Fig. 20 |
| **White scales** | 1 (2.6) | 9 (31) | 1 (1.3) | p<0.001 | Fig. 21 |

Table 5. Dermatoscopic signs, detected in each group in polarized regimen

| **Dermatoscopy with UV-light** | | | | | |
|---|---|---|---|---|---|
| **Follicular signs** | | | | | |
| **UV: keratosis follicularis (white fluorescence of thick follicular lines and clods)** | 0 | 3 (10.3) | 0 | p<0.001 | Fig. 22 |
| **UV: pink follicular dotted fluorescence** | 25 (67.6) | 2 (6.9) | 1 (1.3) | p<0.001 | Fig. 23 |
| **Interfollicular area** | | | | | |
| **Branching blue-red lines** | 0 | 20 (69) | 0 | p=0.02 | Fig. 22 |
| **Disappearance of white clods (pustules)** | 0 | 0 | 6 (75) | p<0.001 | Fig. 24 |

Thus, dermatoscopic structures, seen in acne vulgaris, acneiform rash and exanthematous pustulosis were described. Acne was characterized by following dermatoscopic structures: brown-yellow clods on skin-colored areas (open comedones), white-yellow structureless zones with thin branching vessels, pink srtuctureless zones, white clods surrounded by erythema, scars (white structureless zones) (p<0.001), excoriations (structureless red-brown zones) (p=0.02) and pink follicular fluorescence in UV-light.

Acneiform rush caused by targeten therapy was characterized by yellow clods surrounded by erythema, keratin plug in the center of the pustule, purpura, haemorrhagic spots, keratosis follicularis, pyogenic crusts, pustules surrounded by erythema with teleangiectasia, white scales, in uv-dermoscopy keratosis follicularis was seen as white follicular fluorescence ($p<0.001$), as well as erythema with teleangiectasia ($p=0.02$) and purpura ($p=0.001$).

Acute exanthematous pustulosis was characterized by white clods (pustules) agminated on structureless erythema (Fig. 25). No specific fluorescence in UV-light was detected, althow disapearence of white clods was observed in UV-light (Fig. 24), which were initially visible in polarized light. This could be explained by very superficial localization of pustules in acute exanthematous pustulosis (Fig. 26). Opposite to acute exanthematous pustulosis, in acneiform rashes white clods did not disapper in UV-light (Fig. 27), which can probably be explained by deeper localization of follicular pustules (Fig. 28).

As we can see on diagram (Fig. 28), many dermatoscopic signs can be present in all three assessed skin disorders, including purpura, yellow-white structureless areas with linear vessels, yellow-white clods, surrounded by erythema, pink follicular fluorescence. But at the same time part of dermatoscopic signs was found only in two of three disorders.

For example, yellow clods on a skin-coloured background were previously mentioned as corresponding to open comedoned dermatoscopic structure, which allows to differenciate acne from acneiform rush. In our study yellow clods on a skin-coloured background corresponded also to healing pustules in patients with pustulosis.

Yellow clod in the center of white clod was previously mentioned in the literature as feature, typical for acneiform rush, induced by targeted therapy. In our study we found similar

structure also in patients with acne, althow it was not so prevalent as in patients with acneiform rash.

Haemorrhagic crusts, found in patients with acne and acneiform rash differed in ethiology: in acneiform rash these crusts developed due to fragility of skin slose to hyperkeratotic areas, and in acne patints haemorrhagic crusts were mostly self-induced by patients through excoriations. This was probably the reason, why haemorrhagic crusts were found predominantly in acneiform rush.

And descrete pink structureless areas were found in both acne (most often) and acneiform rash (rarely) as a result of postinflammatory erythema in healing lesions.

And there were some structures that were specific to each skin disorder. For example, only in acne white structureless areas where detected, which corresponded ti scars. Scarring was not observed in pustilosis or acneiform rash. Only in pustulosis we observed white non-follicular clods (pustules), surrounded by structureless erythema, with tendency to merge (25), disappearing in UV-light (24), .

And the disorder with most numerous specific features was acneiform rash. It included follicular keratosis, which was best visible in polarized light in patients receiving MEK-inhibitors, and UV-light significantly enhanced visualization of follicular keratosis which was observed as white thick lines protruding from follicles. Haemorrhagic spots, erythema with irregular linear vessels, and branching vessels in UV-light were observed only in acneiform rash.

Thus, based on the Venn diagram an algorithm of differential diagnosis of acne vulgaris, acneiform rash and acute exanthematous pustulosis based on dermatoscopic signs can be suggested (Fig. 29).

## Discussion

Thus, it has been shown that dermatoscopy can reveal signs specific to acneiform eruptions caused by antitumor therapy. These included structures mentioned previously in the literature (keratin plug in the center of a white clod (pustule)) as well as other structures (keratin plug surrounded by erythema,, purpuric structureless areas, haemorrhagic crusts, erythema with teleangiectasia, haemorrhagic spots (red-brown structureless areas), keratosis follicularis which is very prominent in UV-light, pyogenic crusts, white clods (pustules surrounded by erythema with teleangiectasia, white scales, pustule surrounded by purpura, keratosis follicularis seen in form of white follicular fluorescence in UV-light, and pink follicular fluorescence, seen in in UV-light.

Dermatoscopic signs of acne lesions were characterized earlier as neutral yellow background with central punctim [20]. The presented study gives more detailed description of acne which was characterized by yellow clods (open comedones), white-yellow structureless areas with thin branching vessels, pink structureless ares (post-inflammatory erythema), white clods (pustules) surrounded by erythema, excoriations in the form of a colarette of scales surrounding central pink area, scars in the form of thin vessels on a white-pink background. The last structure was the most specific for acne because it was not observed in other disorders.

Acute exanthematous pustulosis is characterized by monomorphic dermatoscopic manifestations and was characterized by non-follicular pustules (white clods), which are agminated on diffuse erythema, and ths was mentioned earlier in the literature [24]. This study showed also, that these white clods tended to merge in contrast to acne vulgaris and acneiform rash. Besides that, new observation in this work included disappearance of these

white clods in UV-light, which can be explained by superficial character of the pustules and physical properties of UV-light.

In this study, for the first time a comparison of dermatoscopic signs of acneiform rashes due to antitumor therapy, acne vulgaris and a potentially life-threatening disease - acute exanthematous pustulosis was conducted.

Some dermatoscopic signs of acneiform rashes, acne and acute exanthematous pustulosis were mentioned in previously published literature [17,20,23, 24] and coincide with the signs identified in patients of our sample. Among mentioned disorders only acne was assessed with UV-dermoscopy [21,22].

At the same time, this work supplemented and expanded the spectrum of dermatoscopic signs in each disorder, as well as compared the prevalence of each detected structure.

Data analysis using Venn diagram allowed differentiating overlapping and specific dermatoscopic signs, which were included in the first algorithm of differentiation of acneiform rashes with pustules in onciligic patients (acne vulgaris, acneiform rach caused by anti-tumor therapy, acute exanthematous pustulosis).

This study has limitations due to limited number of patients with acute exanthematous pustulosis.

The identified dermatoscopic features of the investigated dermatoses will allow differentiation of rashes in patients receiving antitumor therapy at early stages based on proposed algorithm, both in young patient, which are now more and more often prescribed targeted anti-tumor therapy, and in older patients, which often receive combined therapies including targeted and chemotherapeutic agents which can cause different rashes.

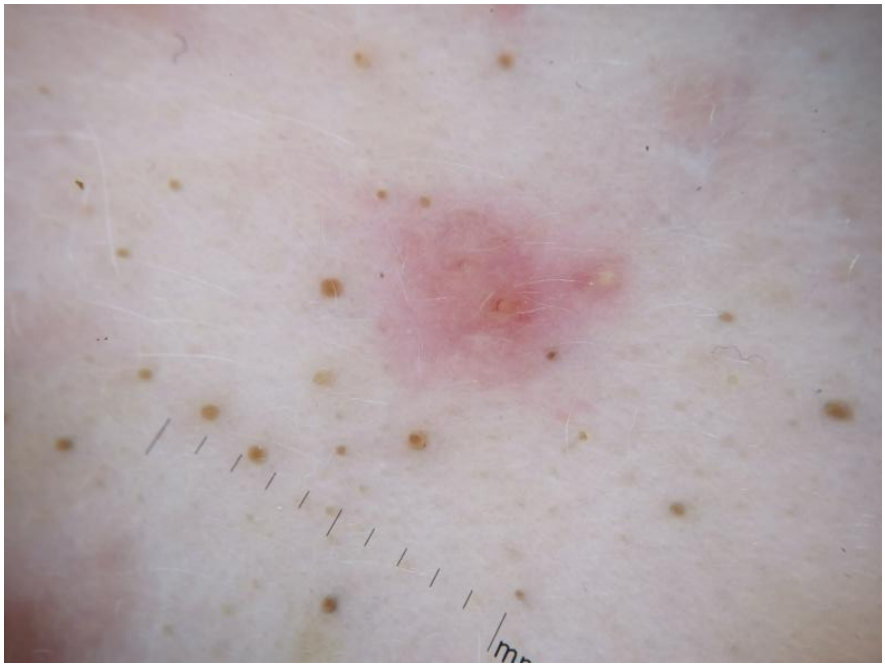


Fig. 5. Yellow clods (open comedoes), pink structureless areas (post-inflammatory macule) in acne

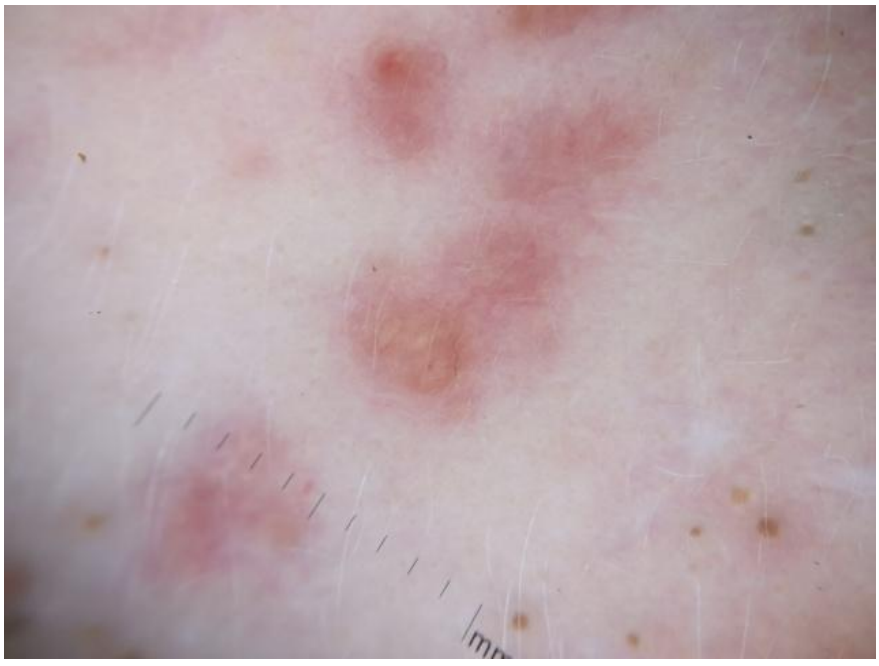


Fig. 6 Yellow structureless areas with thin branched vessels in acne

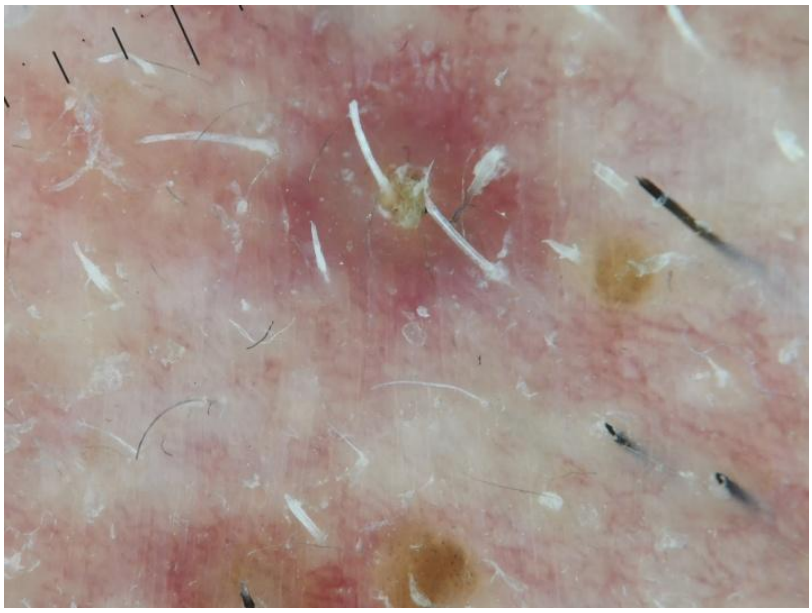


Fig. 7 Yellow clod (follicular plaque), surrounded by structureless pink area (erythema) in acneiform rash

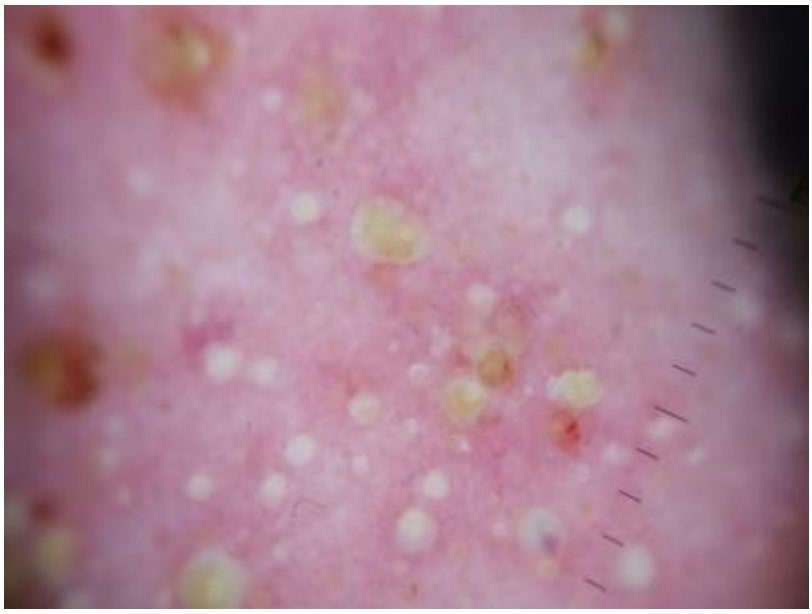
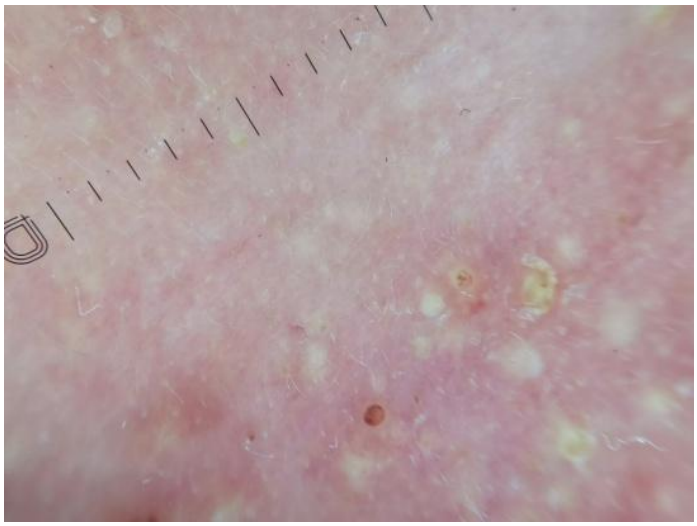


Fig. 8 Follicular keratin plaque in the center of pustule in acneiform rash



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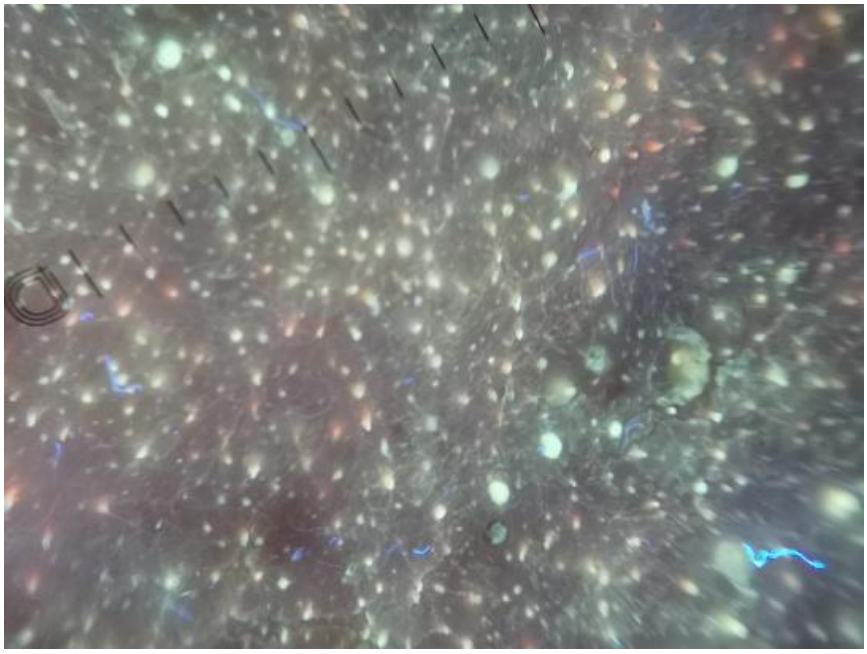


b

Fig. 9 Follicular keratosis in polarized (a, yellow thick lines and clods, follicular) and UV-dermoscopy (b, white and pink lineer fluorescence, follicular) in acneiform rash.

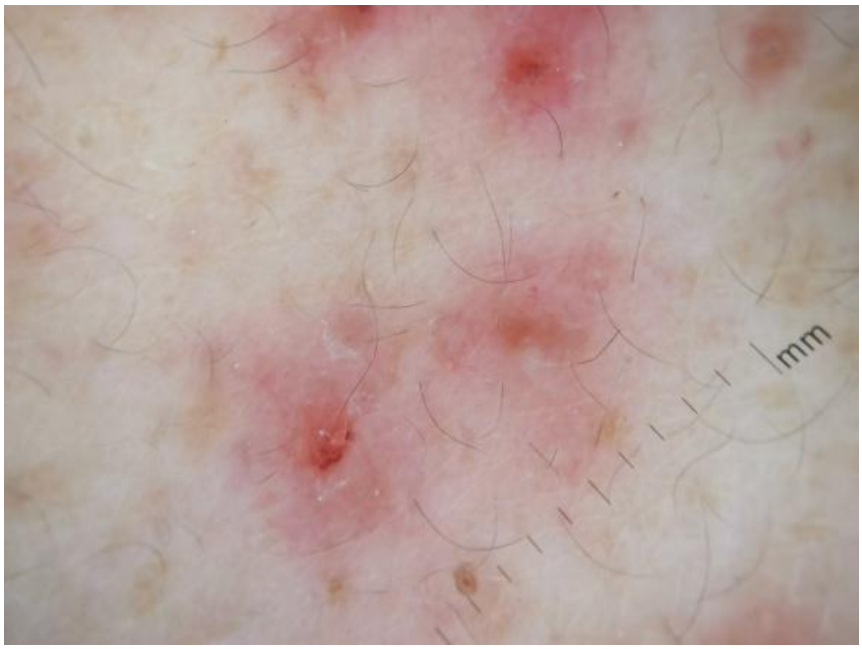



Fig. 10 Purple structureless areas (haemorrhagic spots) in acneiform rash

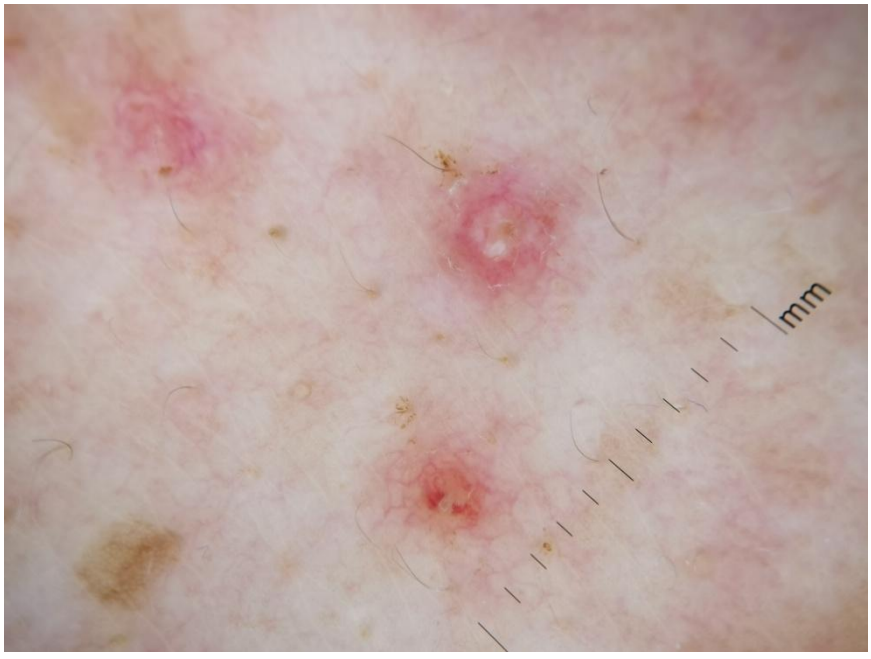



Fig. 11 White and yellow clods (pustules) surrounded by purpura in acneiform rash

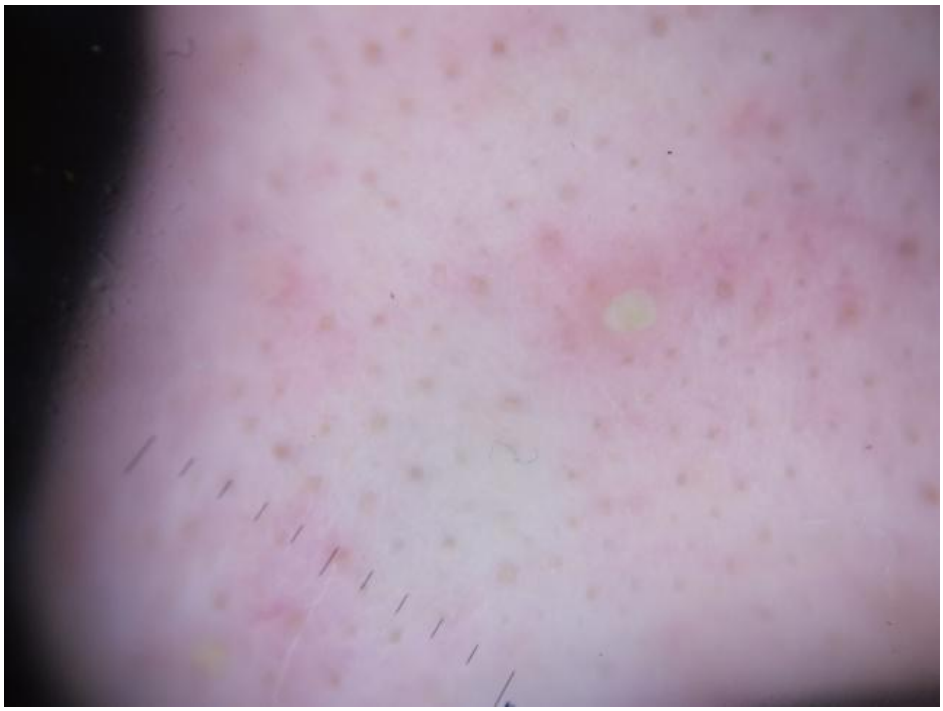


Fig. 12 White clod (pustule) surrounded by structureless red zone (erythema)

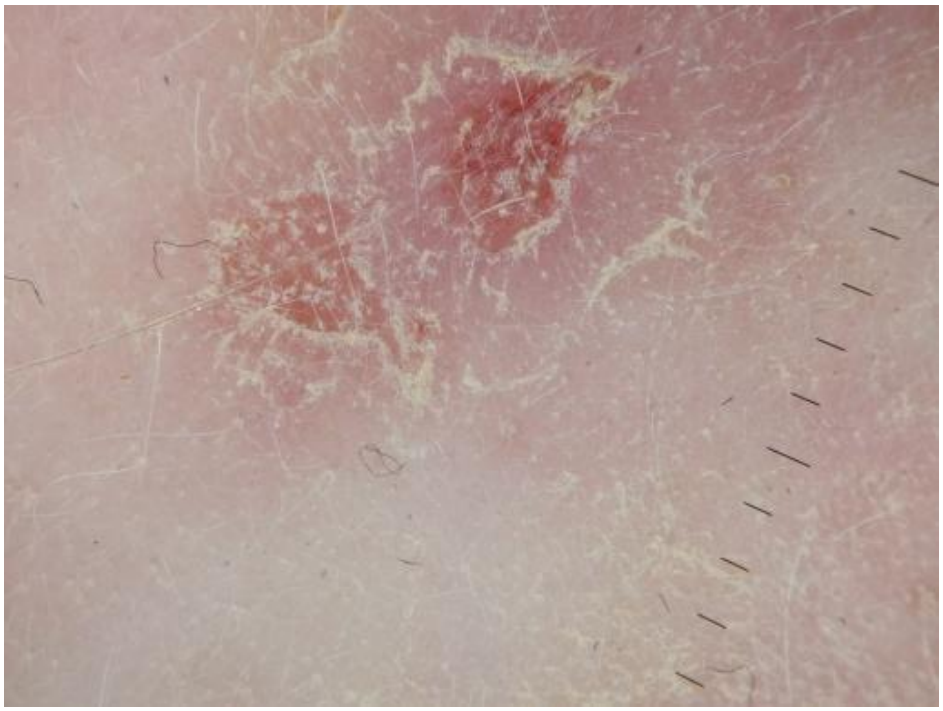


Fig. 13 Srtuctureless red-brown areas surrounded by white scales (excoriation) in acne

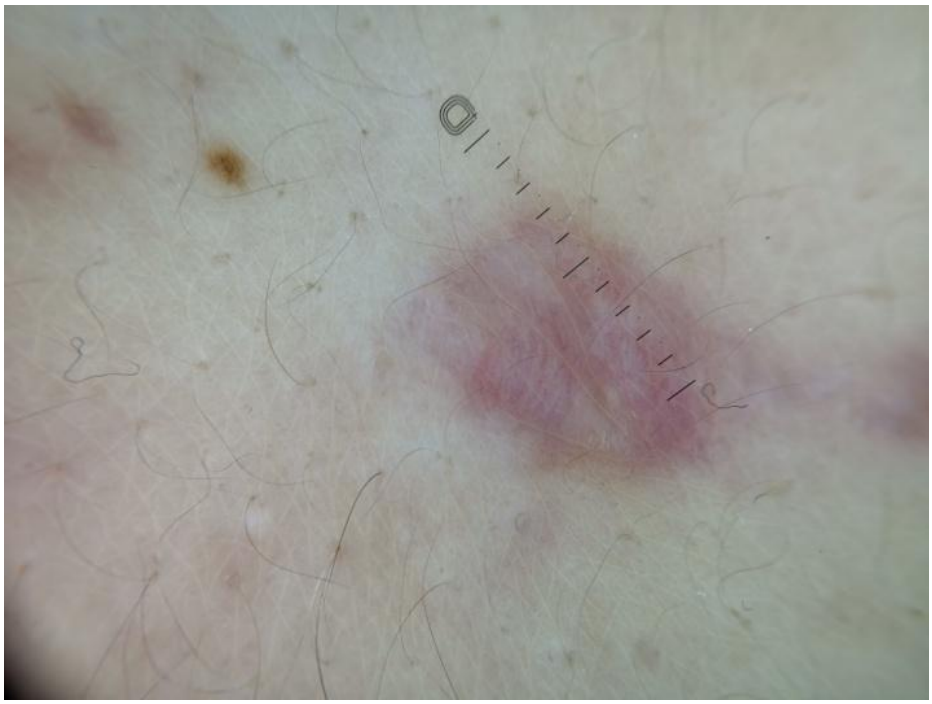


Fig. 14 Scar in acne

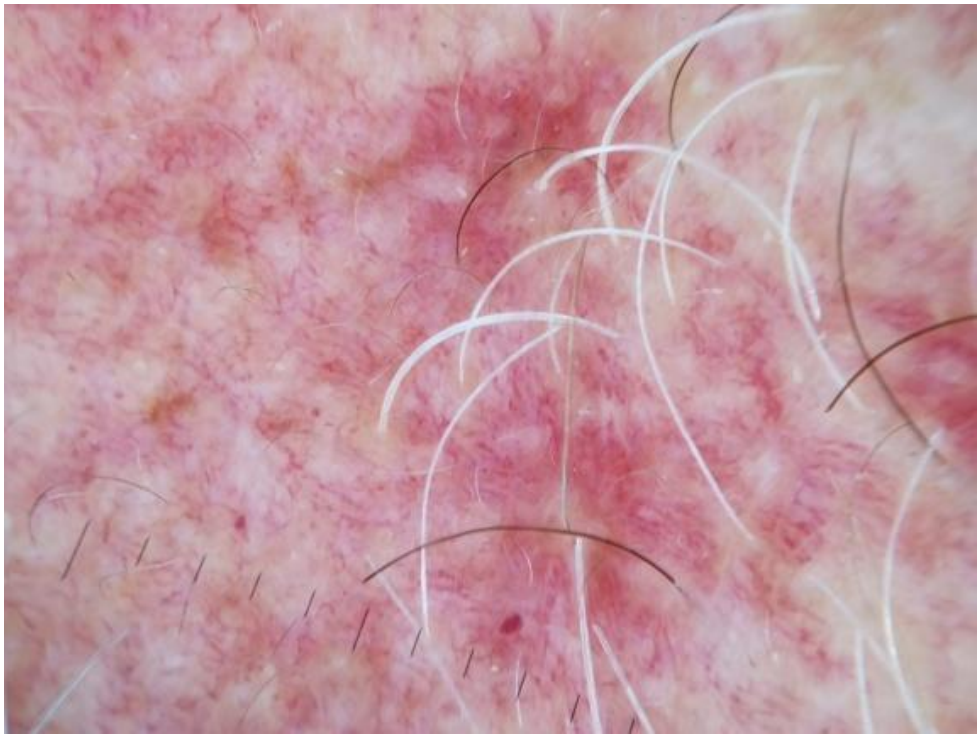


Fig. 15 Thin linear vessels on red background (erythema with teleangiectasia)

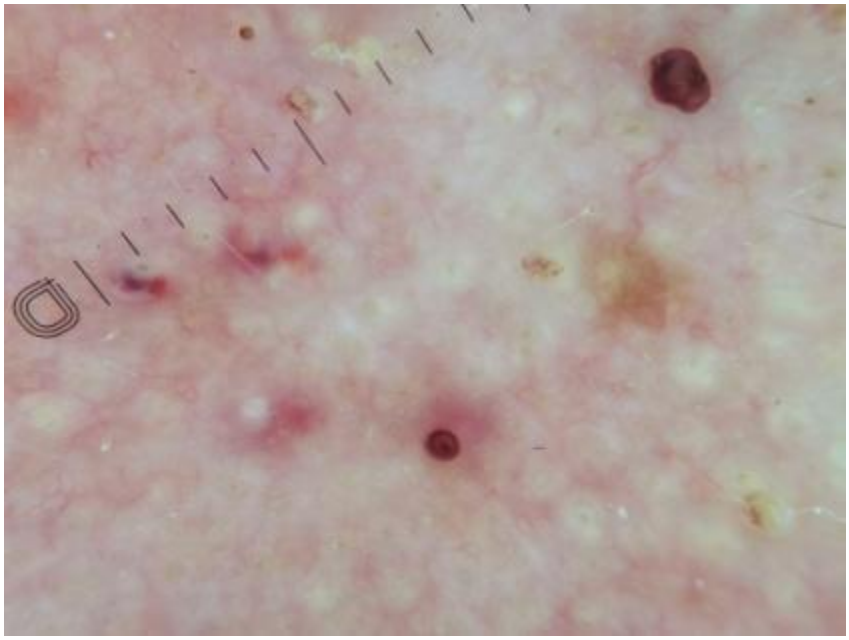


Fig. 16 Purpuric structureless areas with haemorrhagic crusts in acneiform rash

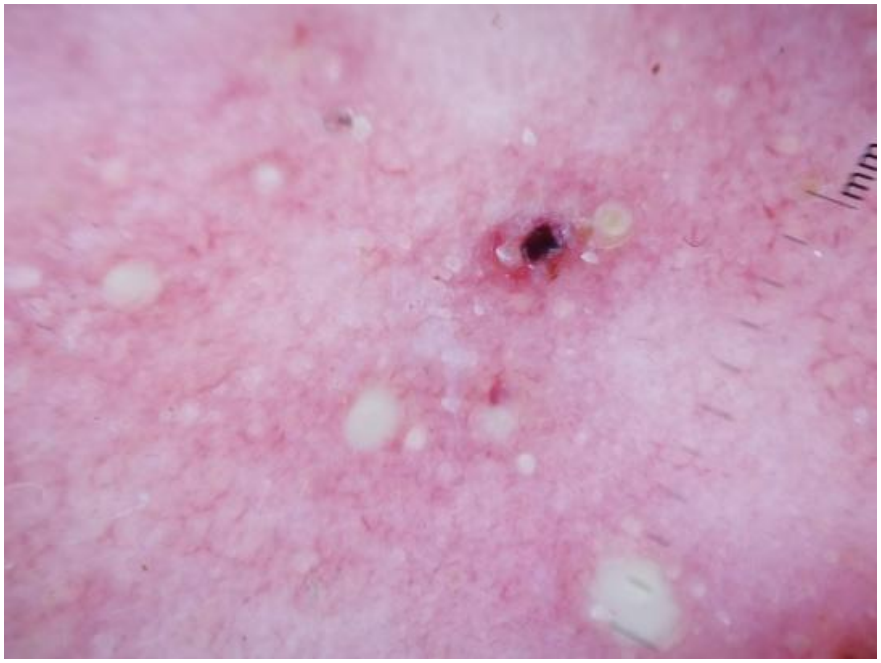


Fig. 17 White clods (pustules) surrounded by thin linear vessels on red background (erythema with teleangiectasia) in acneiform rash

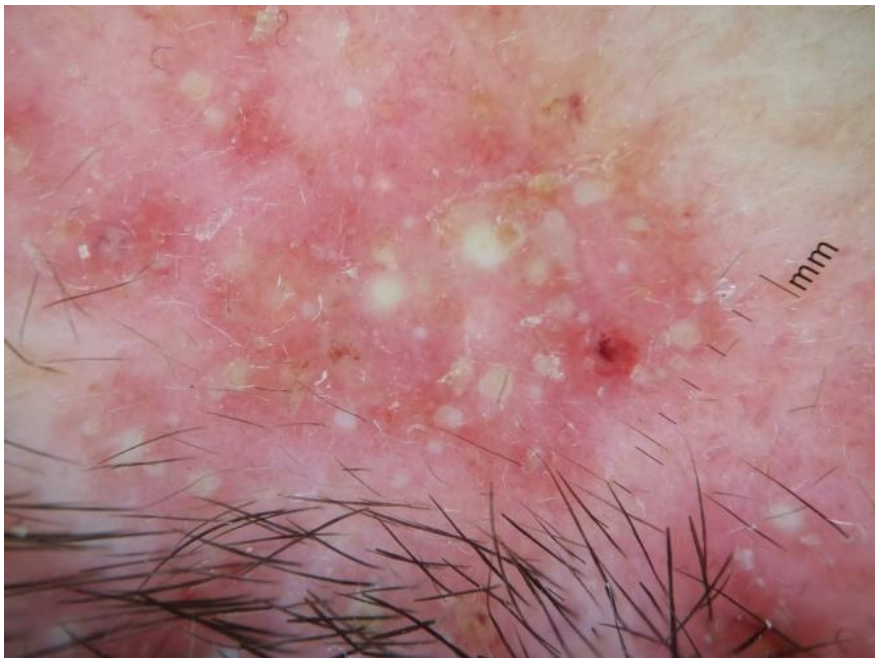
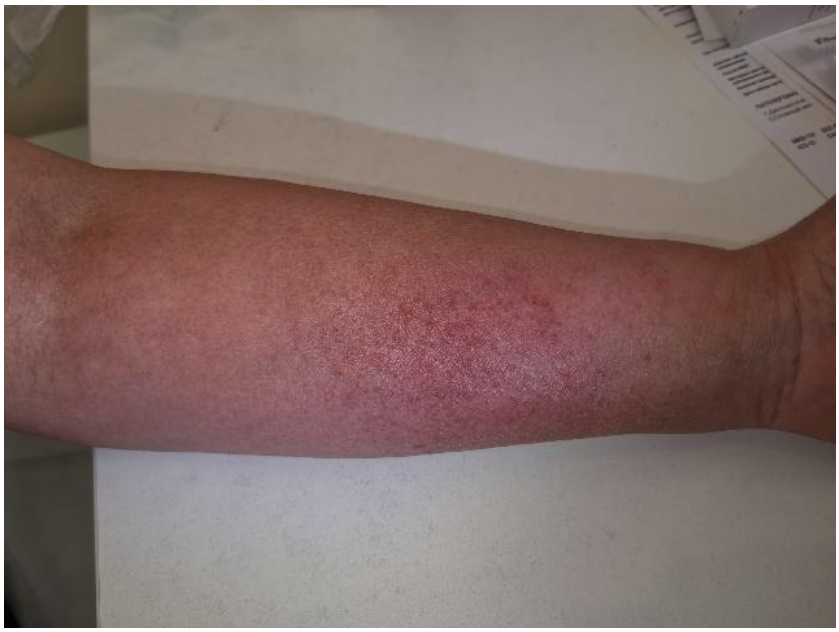



Fig. 18 White clods (pustules) agminated on diffuse erythema in acneiform rash



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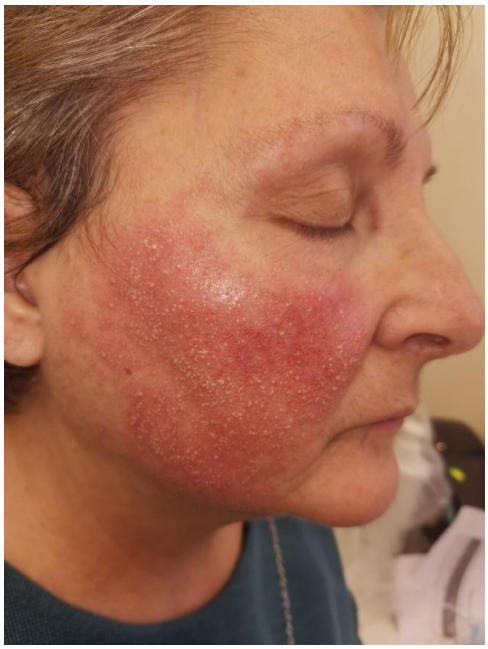

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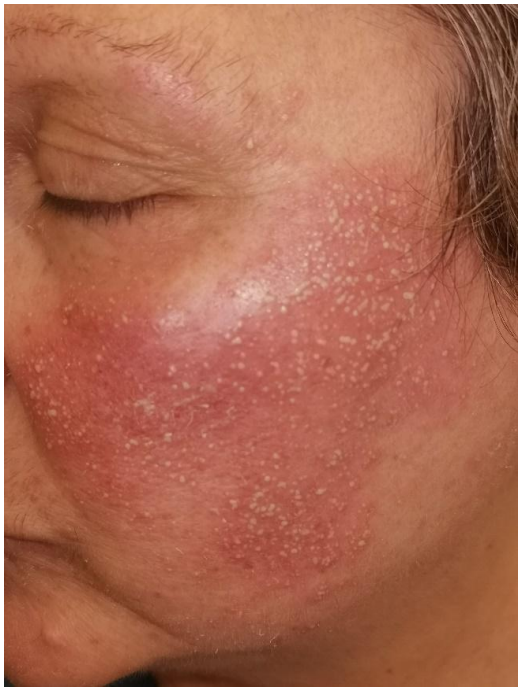

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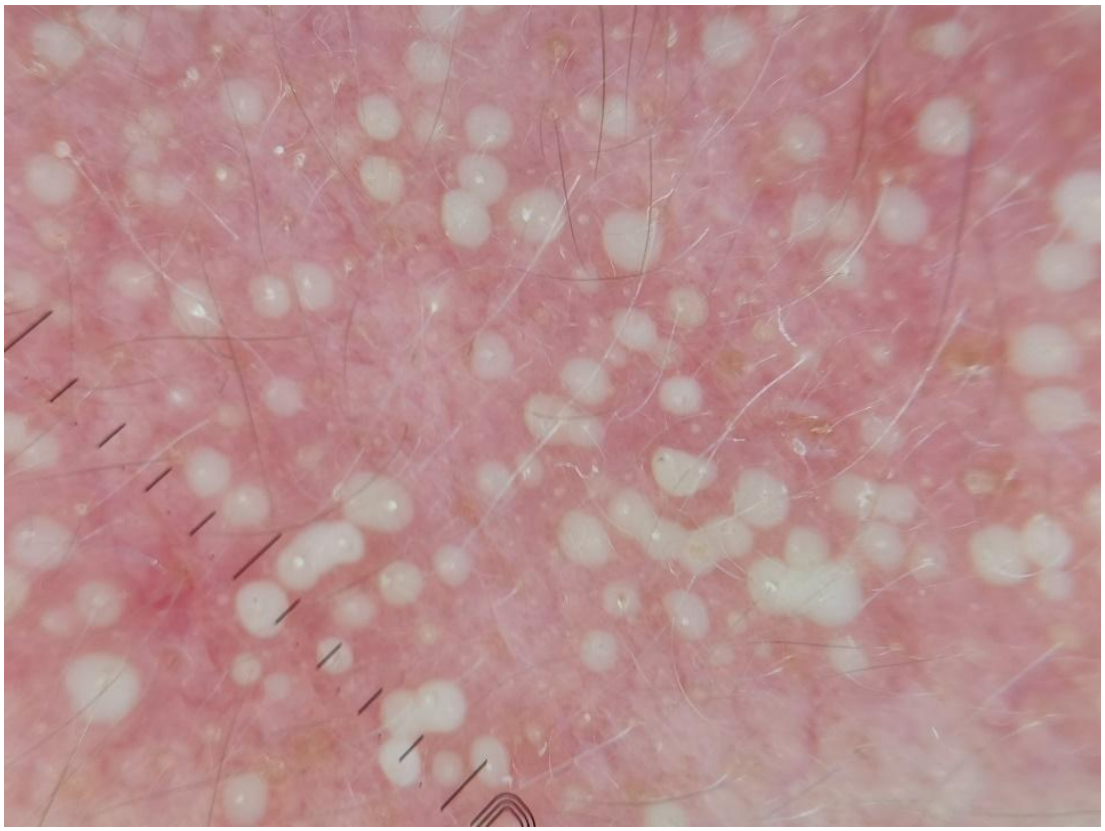


c

Fig. 19. Symmetrical rashes in acute exanthematous pustulosis on the skin of the cheeks (a, b), represented by follicular pustules prone to merging, surrounded by erythema, which is especially clearly visible during dermatoscopy (c) (acute lesions).

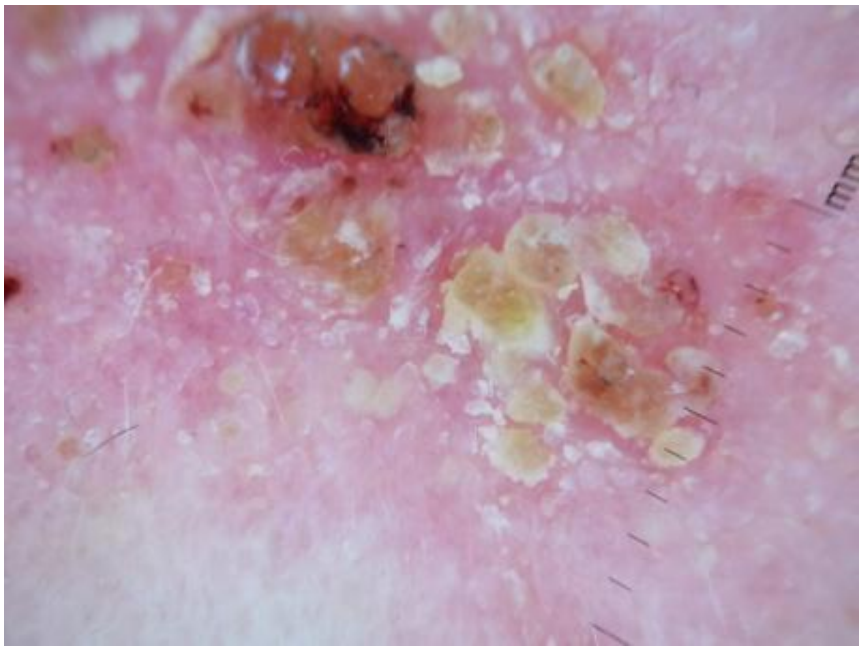


Fig. 20 Haemorrhagic and pyogenic crusts in acneiform rash

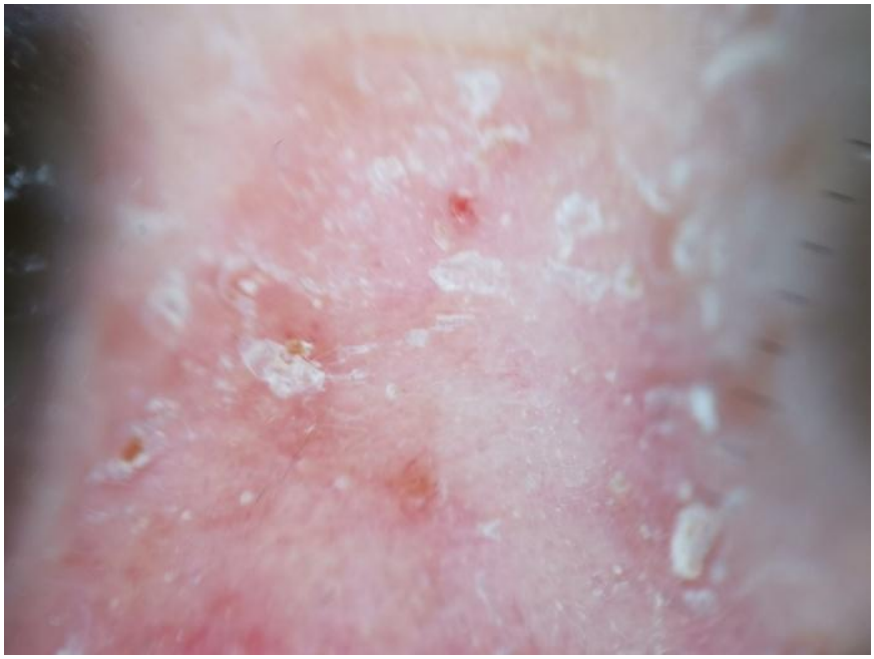


Fig. 21 White scale in acneiform rash

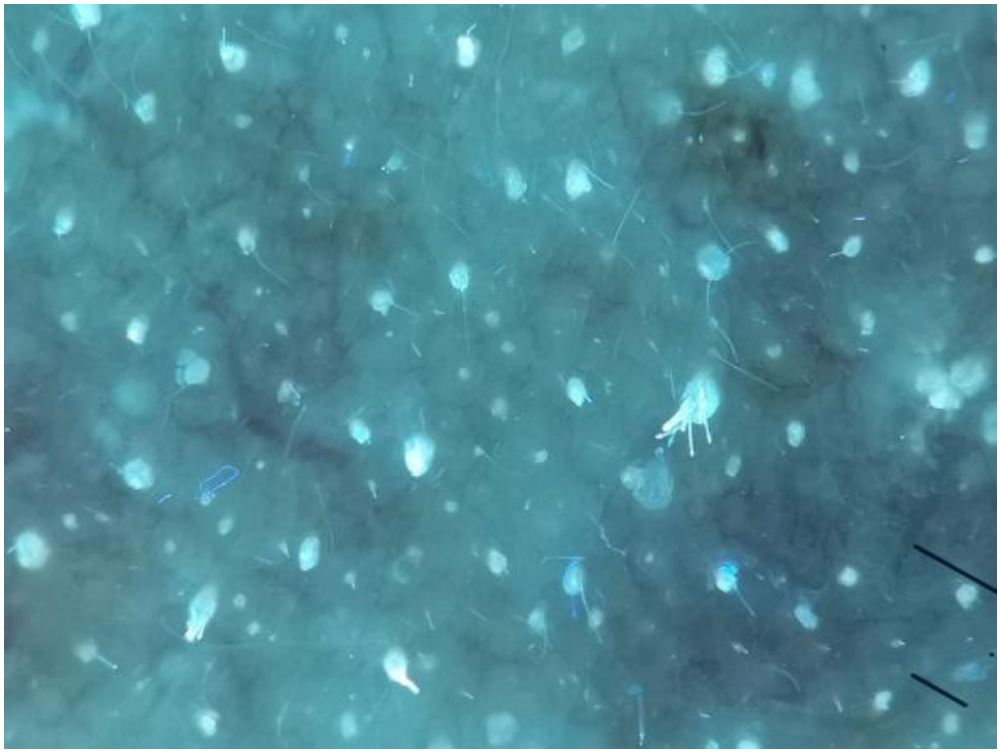
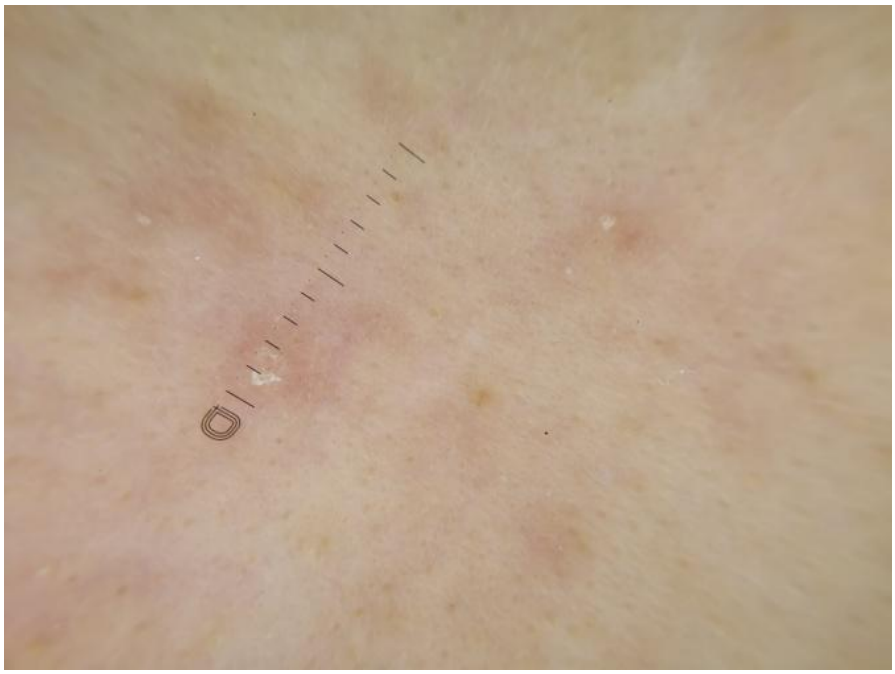


Fig. 22 White fluorescence of follicular keratosis in acneiform rash (thick follicular lines and clods)



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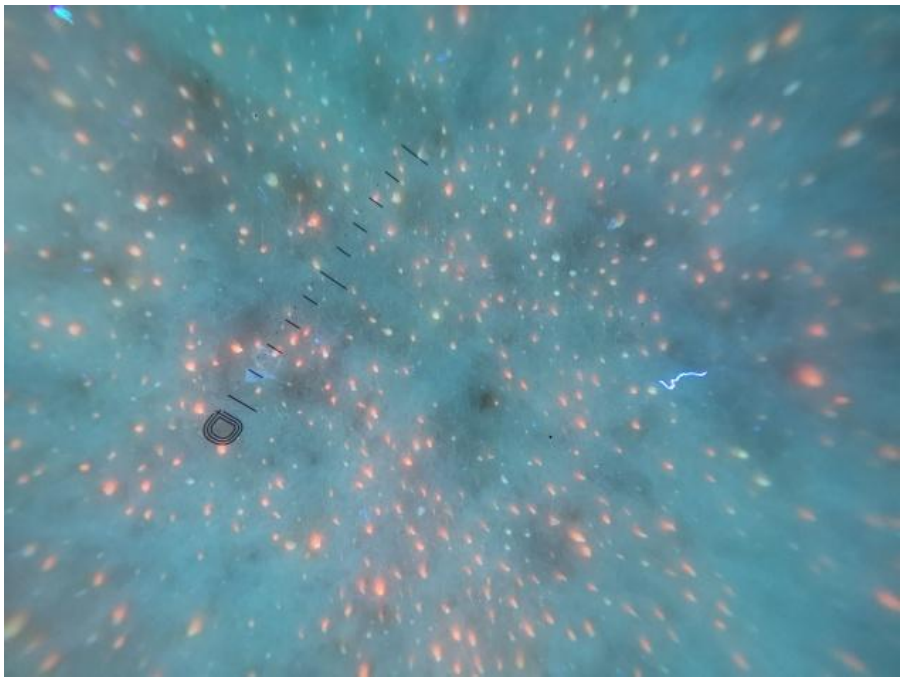
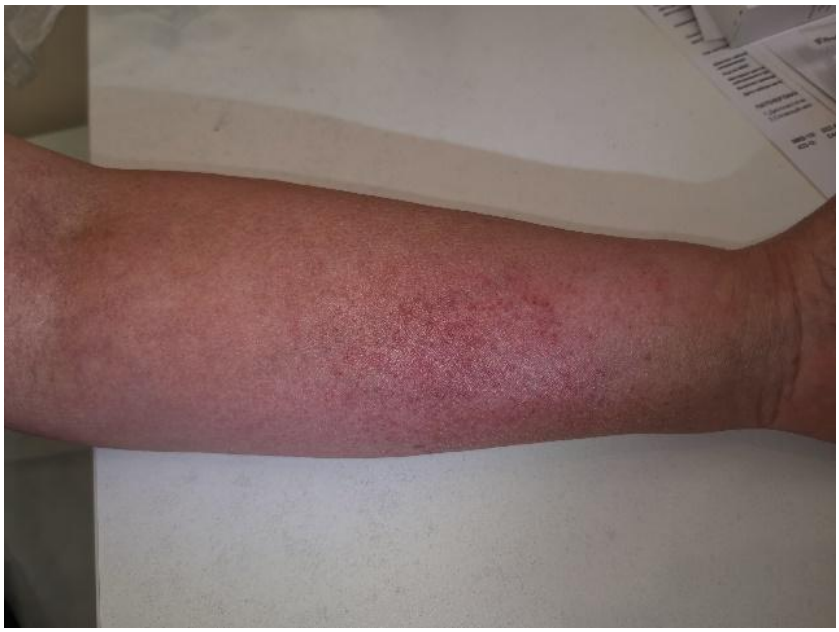
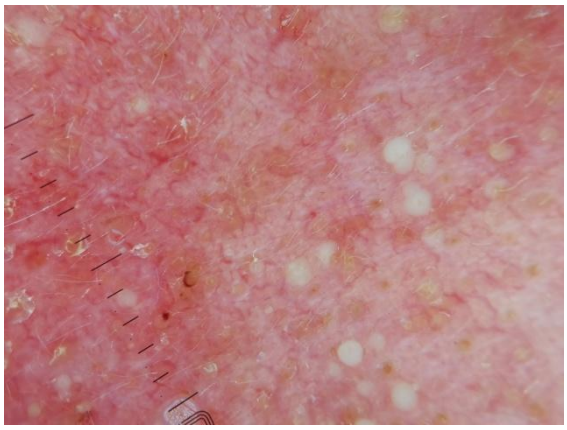


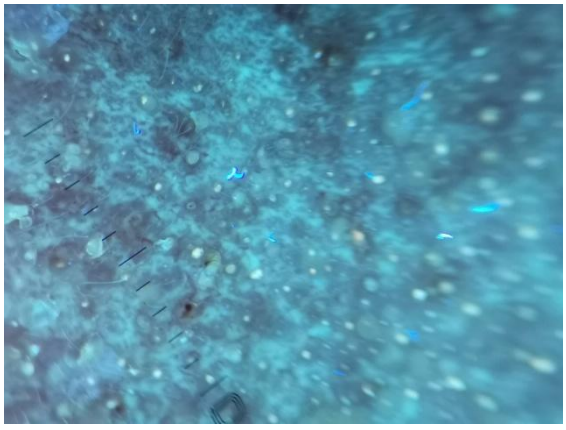
b

Fig. 23 Dermatoscopic signs (a) of white scales surrounded by pink erythema. Pink fluorescence of follicular openings in acne



a





b c

Fig. 24 White clods (non-follicular pustules) surrounded by erythema in acute exanthematous pustulosis (subacute lesions) (a), which are visible in polarized light (b) and “disappear” in UV-light (c).

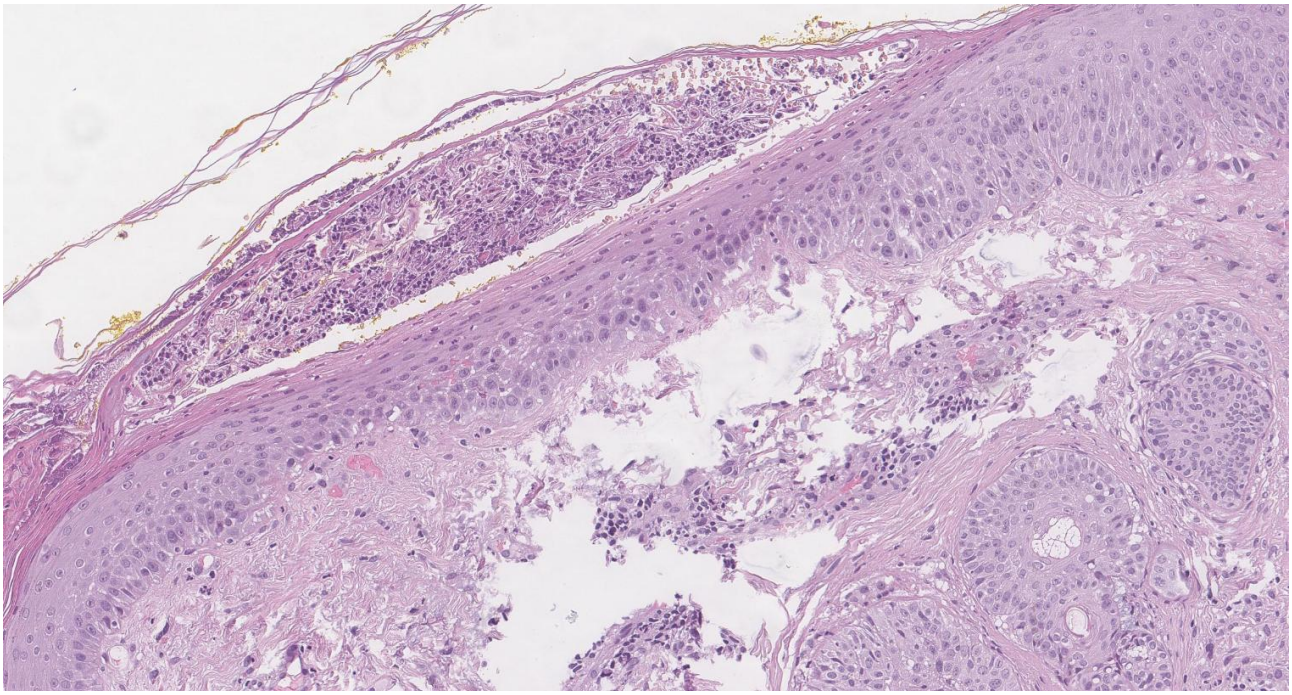


Fig. 25. Pathology of acute exanthematous pustulosis (hematoxilin-eosin, x20).Large accumulations of neutrophils are determined in the thickness of the stratum corneum and the lumens of the hair follicles. In the epidermis, keratinization with parakeratosis, acanthosis, spongiosis with expansion of intercellular contacts and formation of vesicles. In the dermis, inflammatory infiltration of lymphocytes, histiocytes, eosinophils

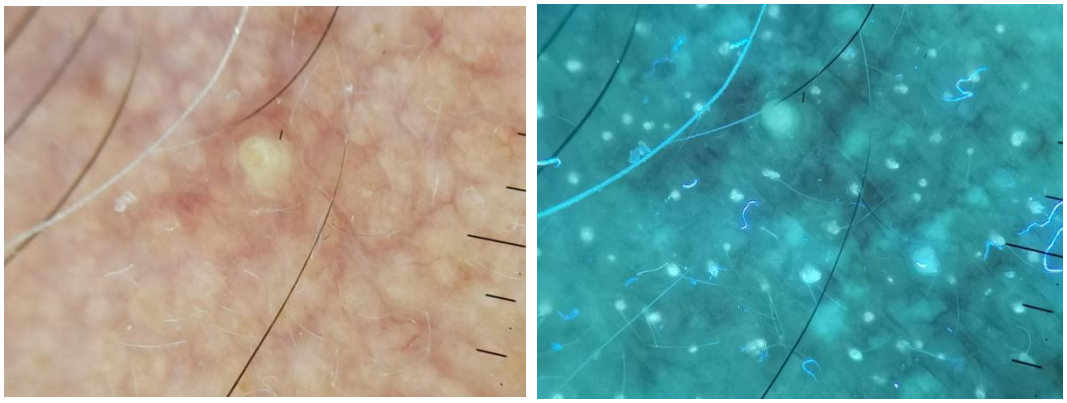


Fig. 26. White clod (follicular pustule) (a), which does not disappear in UV-light (b) and is accompanied by prominent follicular keratosis on surrounding skin, visible in UV-light (in patient with acneiform eruptions due to cancer therapy).

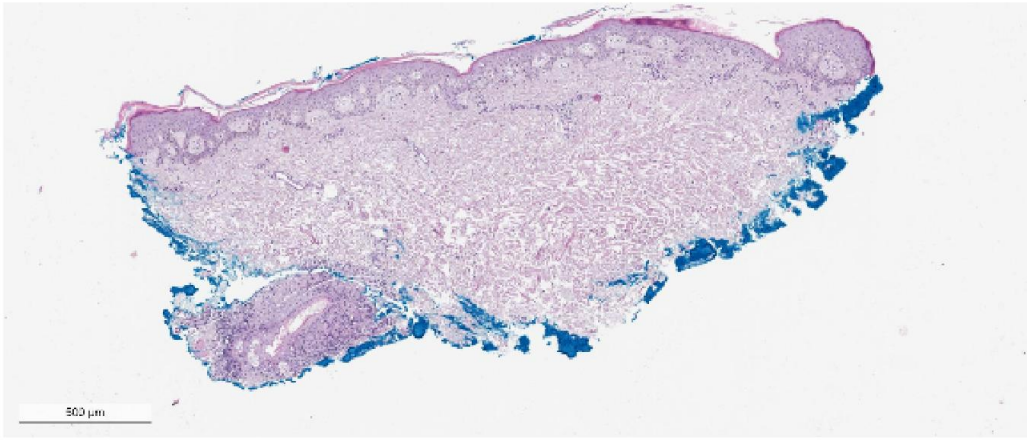


Fig. 27. In the papillary layer there is a minimal perivascular lymphocytic infiltrate ; upon further cutting of the material, a single follicle with a perifollicular lymphohistiocytic infiltrate with giant multinucleated cells was revealed (hematoxilin-eosin).

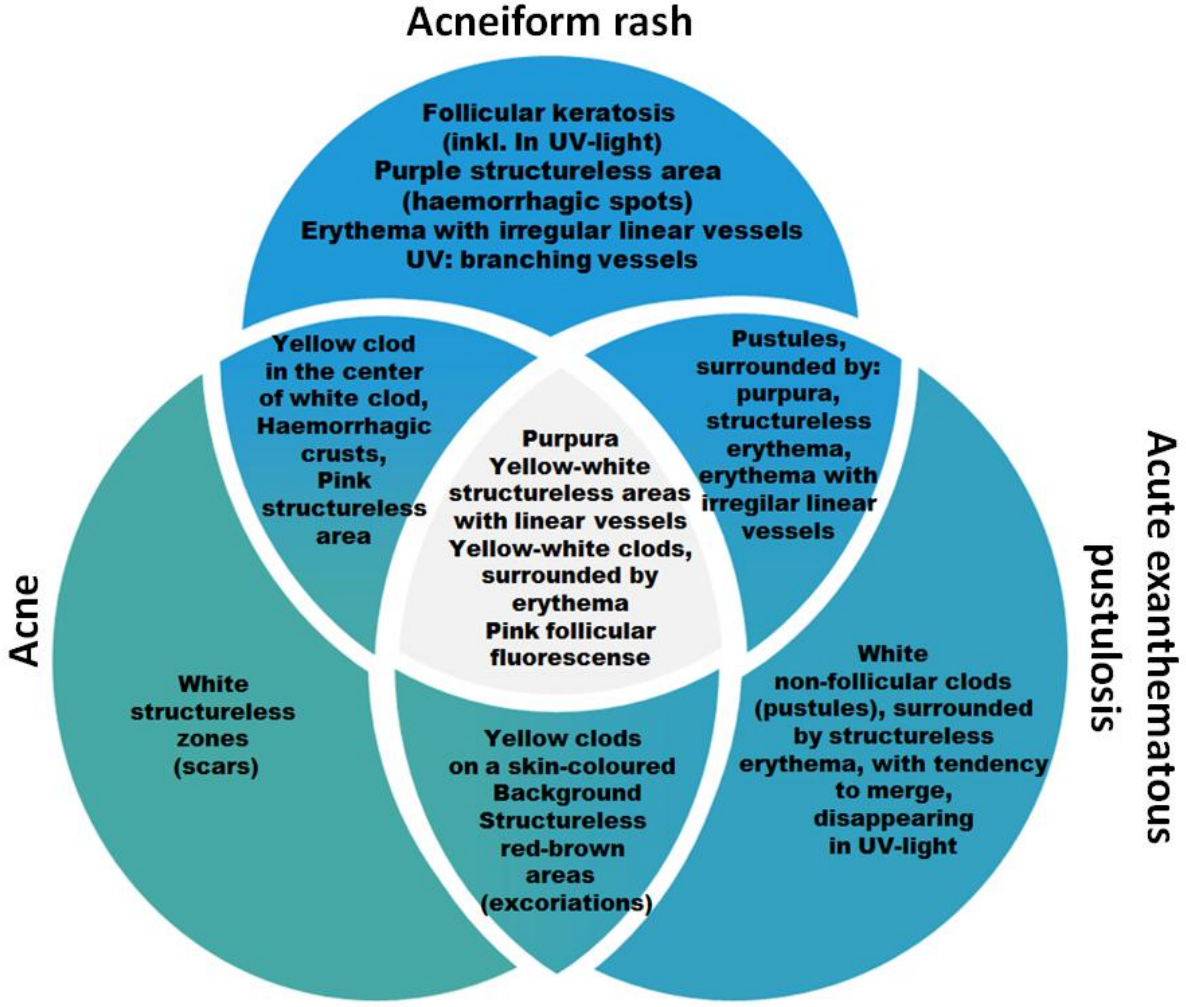



Fig. 28. Venn diagram demonstrating distribution of dermatoscopic structures in patients with acne, acneiform dermatitis and acute exanthematous pustulosis.

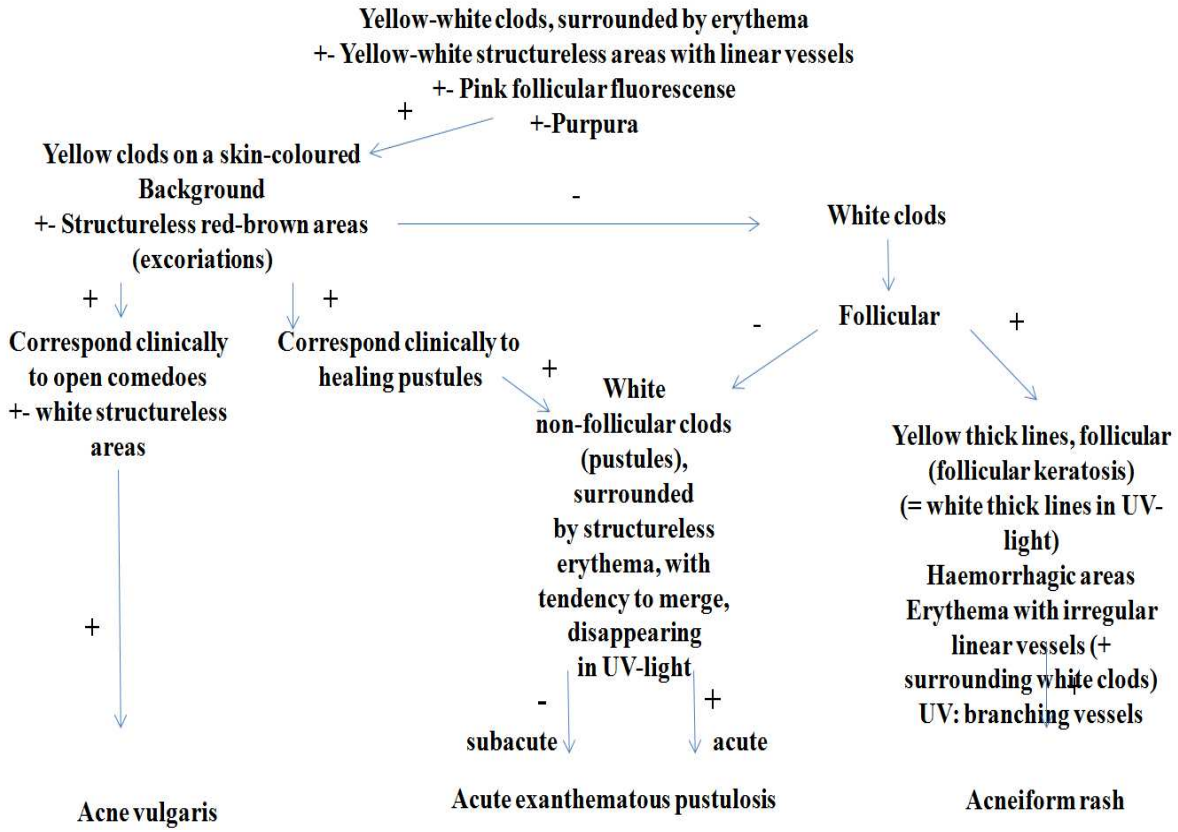



Fig. 29. Algorithm of differential diagnostics of acne, acneiform rash due to targeted therapy and acute exanthematous pustulosis based on dermatoscopic signs.

APPENDIX **1**

## 1. Severity of acneiform rush during antitumor therapy according to CTCAE v. 5.0 criteria

| CTCAE term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Papulopustular rash | Papules and/or pustules covering ≤BSA which may or may not be associated with symptoms of pruritus or tenderness | Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms | Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; IV antibiotics indicated | Life-threatening consequences | Death |

APPENDIX 2

## 2. Assessment of acne severity according to GEA scale

**0: Clear**

**1: Almost Clear**

**2: Mild**: (easily recognizable, less than half of the face involved)

**3: Moderate**: (more than half of the face involved, many lesions)

**4: Severe**: (entire face covered with papules and pustules)

**5: Very Severe**: (highly inflammatory, with nodules)

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