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ACUTE FEBRILE ULCERATIVE CONGLOBATE ACNE WITH LEUKEMOID REACTION

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Abstract. Two cases of acute febrile ulcerative conglobate acne with leukemoid reaction are described. In both cases the skin disease was associated with symptoms of severe systemic disease, e.g. fever, anemia, elevated sedimentation rate and, in one case, arthralgia. The clinical findings in these two cases are compared with those of 23 cases of conglobate acne hospitalized at the Department of Dermatology, Karolinska sjukhuset, during the last 10-year period mainly because of failure of or complication to the conventional outpatient treatment of these patients. The literature on acute febrile ulcerative conglobate acne is also briefly summarized and discussed in view of the authors' experience of the case material presented.

Acute febrile reaction in conglobate acne was apparently first described in 1958 by Burns & Colville (1). Similar cases were reported by Windom et al. (14) in 1961, who pointed out the connection between conglobate acne and arthritis, by Thyresson (13), and by Moshella (9) in 1964. Kelly & Burns (7) have recently introduced the apposite name: "acute, febrile, ulcerative conglobate acne with polyarthralgia" for this syndrome. According to their definition "The features of febrile, ulcerative conglobate acne with polyarthralgia" are as follows: (*a*) sudden onset, (*b*) severe ulceration without cyst formation, (*c*) toxic effects as demonstrated by fever and polyarthralgia, (*d*) failure to respond to the usual antibacterial therapy, and (*e*) favorable response to debridement in combination with steroid therapy."

In their cases "the elevated white blood count, with an increased percentage of polymorphonuclear leukocytes", which may be associated with this acute disorder, was not discussed in detail (11). Recently we have had the opportunity of observing a patient with this syndrome, where the hematologic reaction was so pronounced that leukemia seemed to be indicated (12). Consequently, by giving a report on this case and on one of our earlier cases we wish to point out that a leukemoid reaction may also be included in the symptoms presented by acute febrile ulcerative acne. In order to ascertain how frequently changes in the white blood count may occur in connection with conglobate acne we have re-examined the case histories over a 10-year period (1962–1971) of all the patients who were treated for this disease as in-patients at Karolinska sjukhuset.

CLINICAL CASES

Two Cases with Leukemoid Reaction

Case 1

A previously healthy, 16-year-old schoolboy. His father had had severe acne during adolescence, and his mother suffers from contact dermatitis. For several years the patient had had a mild form of acne vulgaris, and in April 1969 there was a sudden deterioration which developed during 1 week without any noticeable cause. Despite conservative treatment the skin lesions continued to deteriorate and the patient was admitted, for conglobate acne, to the Department of Dermatology, St Göran Hospital, on 21 July, 1969.

Physical examination. There were numerous pustules on the face, chest, nape of the neck, and the upper part of the back. Here and there the pustules were confluent; some had crusts whereas others were squamous. Large crusted, confluent cystic lesions occurred mainly at the temporo-mandibular joints, behind the ears and over the temples. Otherwise his somatic condition was normal.

Hospital course. The day after admission the patient's temperature was 38–39°C. In August pain developed in both knees, the left wrist, back, and over the lumbar region. No objective articular lesions, apart from restricted mobility due to pain. Blood pressure was normal and there was no edema. At the same time the laboratory

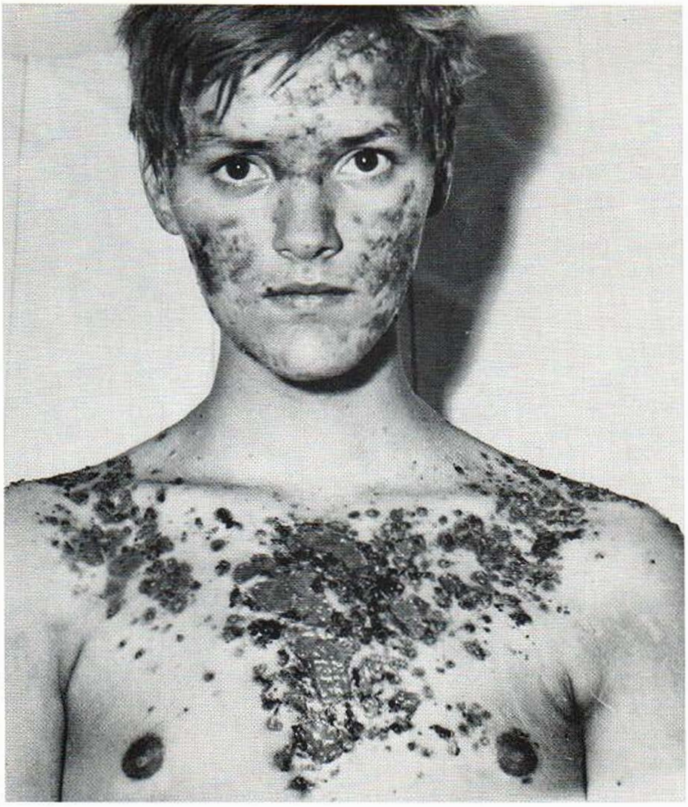

Fig. 1. Case I, August 1969.

findings showed a rise in the ESR, increasing anemia, leukocytosis, and microscopic hematuria. The patient's general condition deteriorated. On August 8 he was transferred to the Kidney Clinic, St Erik Hospital, as suffering from conglobate acne and acute nephritis. Moreover, a hemolytic uremic syndrome was suspected. His temperature continued to vary between 37.5°C and 38.5°C, and he showed signs of increasing fatigue. Kidney biopsy was postponed on account of slightly prolonged bleeding time (a subsequent, complete blood-coagulation test proved normal). On account of increased blood changes, bone-marrow puncture from the anterior, superior spine of the ilium was performed on August 15. Since the bone marrow was considered to show a clinical picture resembling that of myelocytic leukemia ("a highly immature myelopoiesis, with an increase in all forms of young cells down to myeloblasts"), the patient was transferred on August 19 to Medical Clinic III, St Erik Hospital, diagnosed as having leuchaemia myeloides chronica.

Apart from the skin lesions (Fig. 1), the patient's physical condition continued to be normal. Arthralgia remained unchanged. The lymph nodes, liver and spleen were not palpated. This entire development gave reason to question the diagnosis of leukemia and to interpret the blood changes as a leukemoid reaction. On August 25 a new bone-marrow aspiration test was performed (Radiumhemmet, Karolinska sjukhuset), which showed slightly hyperactive marrow with toxic reaction, especially as regards granulocytopoiesis, and a moderately pronounced plasma-cellular reaction. There was no basis for assuming leukemia.

Treatment. Since bacteremia, which possibly originated from the skin lesions, could not be eliminated as a cause of the patient's febrile and toxic symptoms, namely, severe acne, arthralgia, leukemoid reaction, signs of focal nephritis and hepatic complications, antibacterial therapy was introduced (ampicillin i.v. followed by cefalosporine i.v./i.m., from September 10 replaced by tetracycline 0.5 gram × 2 administered orally). From August 27 prednisolone 5 mg × 4 was simultaneosuly administered. The skin was treated by removing the crusted necrotic plaques, topical application of sodium chloride solution, and fusidic acid dressings. Five bottles of blood were administered between August 27 and 29. On September 5 the patient had no fever and both his skin and his general condition were rapidly improving. The patient was discharged on September 18 in good health, with essentially normal laboratory findings.

Laboratory studies. The patient showed substantial but transient hematologic deviations typical of a leukemoid reaction. The WBC increased rapidly to a maximum of 23 200/mm³ with toxic granulation. The differential cell count deviated to the left, and on a few occasions from 0.5 to 1.5% of myeloblasts, promyelocytes and myelocytes were present. The total eosinophil count was 381/mm³. The number of platelets was normal. The hemoglobin value dropped to 7.6 g/100 ml (the lowest value observed). The anemia was hypochromic, serum iron level and TIBC

were both low, bleeding time was slightly prolonged, but otherwise the blood coagulation test was normal. No gastrointestinal bleeding and no signs of pathologic hemolysis were found.

Microscopic hematuria was present in the urine with either no, or only slight, traces of protein, and isolated hyaline casts. Clearance and other renal function tests were normal, intravenous urography and renograms were also normal. The liver findings showed a slight but transient increase of SGOT and SGPT activities and of the serum alkaline phosphatase, and a decrease of prothrombin values.

The ESR was elevated during the entire period, the highest value was 127 mm/hr. Serum electrophoresis showed a pronounced acute reaction with elevated haptoglobin. Acute phase protein + +(+). Rheumatologic tests were normal. A study of the serum immunoglobulins showed increased values of IgA, IgM and IgG. ECG and X-ray films of the heart, lungs and sinuses were normal. Bacteriologic cultures gave no significant results. *S. Albus* was occasionally isolated in sparse growth from the skin lesions. Cultures from the nose, pharynx, sputum and urine were negative, as were repeated aerobic and anaerobic blood cultures. AS 400-500, ASTA 1.4. No signs of foci in the ears, nose and throat.

Re-examination. After discharge, the patient continued to take tetracycline 0.5 g × 2 and prednisolone 5 mg × 3. During this treatment slight Cushing's syndrome developed and the acne lesions healed. When admitted for re-examination in October 1969 there were no signs of acne activity, but keloidal formations on the chest, back, and face were observed (Fig. 2). All the laboratory findings and bone-marrow examination were normal, and the bacteriologic tests negative. After final discharge the patient continued to visit a dermatologist for regular check-ups until February 1970 during which time therapy was gradually withdrawn.

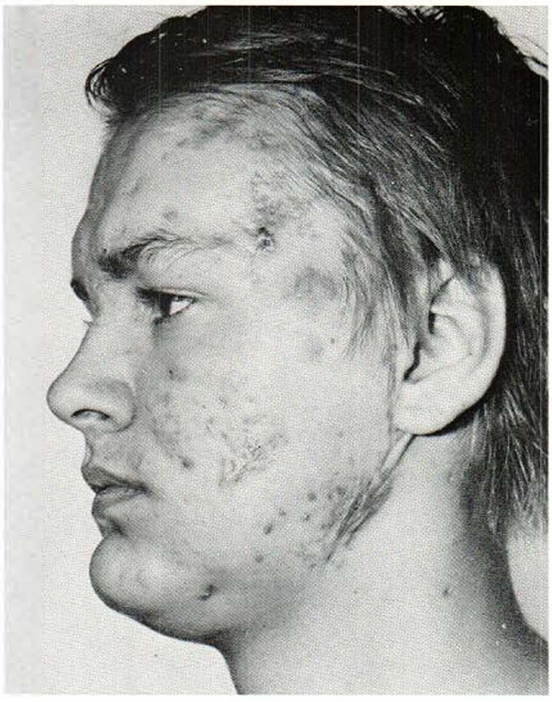

Fig. 2. Case I, October 1969.

Case II

A previously healthy 15-year-old schoolboy. His father had had severe acne during his adolescence. Since the age of 12 the patient has had mild acne vulgaris, with eruptions on the face and shoulders. On January 31, 1959, he fell ill with morbilli. There were no complications. He began school on February 11 and felt perfectly healthy. On February 16 there was acute deterioration of the acne lesions. Headache and fever, after two or three days increasing to over 39°C. The patient was given penicillin therapy at home. On February 20 he was admitted to the ward for infectious diseases as septicemia was suspected, and on March 3 he was transferred to the Department of Dermatology, University Hospital, Uppsala.

Physical examination. The skin of his face was almost completely covered with yellow smeary crusted plaques, and here and there on his cheeks were oval, subcutaneous, fluctuating infiltrates. The shoulders and chest were covered with numerous navicular pustules and crusted plaques and sores. Similar, but minor, lesions were present on the upper arms, buttocks and scalp.

Clinical course. Despite immediate introduction of erythromycin therapy a high temperature between 38–39°C continued from February 20 to March 9. Triamcinolone therapy was started on March 10, and the temperature then dropped to 37°C. Subsequently, the patient remained afebrile during his entire hospital stay. No arthralgia. Primarily, septicemia was suspected, but repeated blood cultures proved negative. Severe leukocytosis, with more than 30 000 WBC/mm^3, gave cause to suspect leukemia. Bone-marrow smears showed high activity, but afforded no definite basis for this diagnosis.

Laboratory studies. Leukocytosis, varying between 20 000 and 33 000 WBC/mm^3, during the period from February 20 to March 18. After that there was a gradual normalization. Substantial deviation to the left, with abundant toxic granulated polymorphonuclear leukocytes. Total eosinophil count was approximately 300/mm^3. Platelets approximately 200 000/mm^3. Hemoglobin value 11–12 g/100 ml. RBC 3.8–4.0 million. On admission the ESR was 90 mm/hr, and on discharge 23 mm/hr.

Blood cultures negative. Bacterial cultures from the pharynx and pustules: sparse growth of *S. albus*. Widal's reaction and the Paul-Bunnel reaction were negative. Urine: on some occasions slight microscopic hematuria. Albumin negative.

Treatment. Erythromycin, 500 mg × 4 daily, had no effect on his temperature. Triamcinolone, 4 mg × 6 daily, produced a dramatic recovery and normalization of temperature. After 3 days the dose was decreased to 3 mg × 4, and was still further reduced during the following weeks. When the patient was discharged medication could be discontinued entirely.

Reexamination. The patient was examined regularly during the following 6 months. His general condition was

Table I. *Cases of conglobate acne, Dept. of Dermatology, Karolinska sjukhuset, Stockholm, 1962–1971. Clinical symptoms*

Case no.	Sex	Age	Acute onset of symptoms	Fever	ESR	Ulcerative skin lesions	Polyarthralgia	Leukocytosis	Hematuria	Remarks
1	♂	18	–	+	42	+	–	25 200	–	Sternal puncture
2	♂	14	–	–	5	–	–	9 900	–	
3	♀	14	+	+	63	–	+	15 400	–	Tietze's syndrome
4	♂	18	–	–	4	–	–	11 700	–	
5	♂	25	–	–	18	–	–	7 800	–	
6	♂	16	+	+	145	+	+	18 200	–	Sternal puncture
7	♂	18	+	+	58	+	–	10 100	–	Mononucleosis; hospitalized 2 times
8	♀	24	–	–	22	–	–	—		
9	♂	18	–	–	11	–	–	14 900	–	
10	♀	25	–	–	22	–	–	7 900	–	
11	♂	19	+	+	84	+	+	12 000	+	Sternal puncture; hospitalized 3 times
12	♂	15	+	+	76	+	–	16 900	–	
13	♀	18	–	–	18	–	–	6 100	–	
14	♀	26	–	–	9	–	–	6 800	–	
15	♀	19	–	–	90	–	–	13 000	–	Sternal puncture; tonsillitis
16	♀	33	–	–	48	–	–	11 400	–	
17	♂	17	–	–	?	–	–	11 000	–	
18	♀	16	–	–	17	–	–	6 600	–	
19	♂	20	–	–	32	–	–	10 200	–	
20	♂	21	–	–	4	–	–	7 300	–	
21	♂	29	–	–	20	–	–	7 500	–	
22	♂	18	–	–	32	–	–	19 700	–	
23	♂	19	–	–	30	–	–	9 500	–	

excellent. He had from slight to moderate acne vulgaris, approximately similar to his condition before the acute deterioration.

Twenty-three Hospitalized Patients, 1962–1971

All the patients were admitted to the Department of Dermatology, Karolinska sjukhuset, during 1962–1971. In the majority of cases indication for admission had been unsatisfactory results of ambulant treatment of acne conglobata whose course had otherwise been normal. Moreover, some of the patients had had general symptoms which required hospital care. Table I shows the most important clinical symptoms. Tables II–IV give the patients' age and sex, the ESR and the occurrence of leukocytosis. As can be seen in Table I general symptoms, especially fever and raised ESR, occurred in 6 patients, 5 of whom were males. All 5 men had ulcerative skin lesions. The female patient and 2 of the males showed signs of arthralgia. The ESR was markedly or greatly raised in all these 6 patients. Two other female patients (nos. 15 and 16) had no general symptoms but a greatly elevated ESR (90 and 48 mm/hr respectively). In patient 15 the raised ESR was probably due to simultaneous occurrence of tonsillitis with beta-hemolytic streptococci.

Table II. *Cases of conglobate acne, Dept. of Dermatology, Karolinska sjukhuset, Stockholm, 1962–1971. Age and sex distribution*

Age	⩽15	16–20	21–25	⩾26	Total
Male	2	10	2	1	15
Female	1	3	2	2	8
Total	3	13	4	3	23

Brief Summary of the 6 Patients with General Symptoms

Case 1. Male aged 18 years treated from March 14 to April 11 1963. The patient had had acne vulgaris for 2 years. After New Year 1963 gradual deterioration and

Table III. *Cases of conglobate acne, Dept. of Dermatology, Karolinska sjukhuset, Stockholm, 1962–1971. ESR mm/hr*

ESR	≤20	21–40	41–60	61–80	81–100	>100	Total
Male	6	3	2	2	1	1	15
Female	3	2	1	–	1	–	7[a]
Total	9	5	3	2	2	1	22[a]

[a] 1 missing.

Table IV. *Cases of conglobate acne, Dept. of Dermatology, Karolinska sjukhuset, Stockholm, 1962–1971. Leukocytes/mm³*

Leukocytes	<10 000	10–15 000	15–20 000	20–25 000	>25 000	Total
Male	5	6	3	—	1	15
Female	4	2	1	—	—	7[a]
Total	9	8	4	—	1	22[a]

[a] 1 missing.

cystic acne with small ulcerative lesions developed on his back. During hospital stay his temperature varied between 37 and 38.5°C over a 10-day period. During the entire hospital time leukocytosis varied between 14 900 and 25 200 cells/mm³. Substantial deviation to the left, with toxic granulation. Bone-marrow aspiration from the sternum: reactive changes without any sign of leukemia.

Case 3. Girl aged 14 years. In hospital from February 4 to March 13 1964. In connection with a throat infection in the autumn of 1963 comparatively rapid onset of conglobate acne on the face. No ulcerative skin lesions. Temperature varied between 37–38.5°C for 1 week. During the entire hospital stay leukocytosis varied between 10 700 and 15 400 cells/mm³. Acute tenderness on the chest was interpreted as a costochondral junction syndrome (Tietze's syndrome).

Case 6. Male aged 16 years. Treated from January 7 to February 26 1965. Symptoms of acne since the age of 13. During spring 1964, repeated infections in the upper respiratory tract. After a similar infection in the autumn of 1964, acute deterioration and development of cystic ulcerative acne on the face and back.

During the first 2 weeks in the department the patient's temperature varied between 38 and 39°C, and then gradually became normalized. Leukocytosis rose to 18 200 cells/mm³, and on discharge on February 26 was 9 400 cells/mm³. There was substantial deviation to the left and toxic granulation. Bone-marrow aspiration from the sternum: highly active marrow without definite signs of leukemia. On January 8 ESR was 70 mm/hr; on January 21 145 mm/hr; and on February 23 46 mm/hr.

Case 7. The patient was treated for the first time from December 5 1960 to January 20 1961; and for the second time from January 25 to February 19 1965. On the first occasion he was 14 years of age and had had acne on the chest, back, and face for the past 2 years. In September 1960 rapidly increasing pustular lesions developed on the chest, face, and back; subsequently the lesions became ulcerative. On admission he was subfebrile; during the next few days his temperature was between 38 and 40°C. ESR fluctuated between 52 and 38 mm/hr. Leukocytes 11 000 cells/mm³. High degree of deviation to the left in the differential cell count. When discharged, the patient's condition had distinctly improved. Subsequently the acne lesions were of medium severity. At the turn of 1964–1965 the patient contracted infectious mononucleosis. After he had recovered from the infection the acne conglobata became acute. This time, however, the ulcerative lesions were only small. No fever. ESR 58 mm/hr. Leukocytes 10 100 cells/mm³.

Case 11. The patient was treated three times for acne conglobata with general symptoms: from October 13 1960 to February 6 1961; from February 21 to April 7 1964; and from March 31 to May 13 1965. On the first occasion the patient was 16 years of age. He had presented symptoms of acne vulgaris for 1 year. Rather rapid onset of skin deterioration, with some ulcerative lesions, occurred in the autumn of 1960. There was increasing pain in the shoulder and hip regions: restricted joint movements. On admission ESR was 95 mm/hr, and later rose to 127 mm/hr. Leukocytes (maximum) 16 800 cells/mm³. Bone-marrow aspiration from the sternum: nonspecific increased activity. When discharged, his condition was greatly improved. On admission in 1964, conglobate acne of medium severity, without ulcerative lesions. ESR still very elevated, between 48 and 84 mm/hr. Leukocytes 12 000 cells/mm³. Intermittent microscopic hematuria.

When treated in 1965 the patient had small ulcerative lesions and complained of pain in the chest muscles. ESR 25–60 mm/hr. Leukocytes 11 100 cells/mm³.

Case 12. Male aged 15 years. Treated from November 11 to 28 1966. About 3 weeks before admission acne pustules spread over chest, back, and nape of neck. His temperature rose to 39°C; simultaneous diffusion of ulcerative skin lesions. ESR on November 11 76 mm/hr, on November 24 38 mm/hr. Leukocytes on November 11 16 900 cells/mm³; on November 28 6 600 cells/mm³. Rapid improvement during hospital stay.

DISCUSSION

The picture of acute, febrile ulcerative conglobate acne has been discussed in dermatological literature since 1959. The syndrome has recently been more clearly defined by Kelly & Burns (7) who, like previous authors, especially stress that joint involvement occurs in acute toxic acne. However, the most striking feature of our material is the leukemoid reaction, which is described more fully in cases I and II. This reaction has never been previously reported in the literature. In the review of our conglobate-acne

material, in which 6 patients showed general symptoms with fever and raised ESR, leukocytosis in 13 out of 22 patients exceeded 10 000 cells/mm³. In several patients the white blood picture was stated to show a deviation to the left, and toxic granulation; and in some cases the bone-marrow aspirations demonstrated nonspecific, reactive changes.

Generally speaking, a leukemoid reaction means the occurrence of morphologic changes in the circulating blood, which resemble those seen in leukemia, but which are not the result of leukemic disease (8). The change may be manifested either in excessive leukocytosis or in the abnormal occurrence of immature types of cells in the circulating blood or in both. Most often this change is of a myeloid type (5). The differential diagnostics against leukemia may prove very difficult, if not impossible, and will not be discussed in detail here. This is because the clinical symptoms and other concomitant hematologic changes, such as anemia and sometimes thrombocytopenia, may also very closely resemble leukemia (15). The bone-marrow changes are of a nonspecific nature.

Leukemoid reactions have been described as occurring especially under the following conditions (15):

1. Infections: i.e., pneumonia, meningococcal meningitis, sepsis, tuberculosis.

2. Intoxications: i.e., eclampsia, severe burns, mercury poisoning.

3. Malignant diseases:

(*a*) usually with bone-marrow metastases, but also without these lesions, i.e., carcinoma of the stomach, colon, lungs, and kidneys.

(*b*) multiple myeloma, myelofibrosis, Hodgkin's disease, reticulosarcoma.

4. Severe loss of blood or sudden hemolysis.

The pathogenesis of leukemoid reactions is not clearly known. Several causative mechanisms have been postulated. Hill & Duncan (4) suggested for example, at an early stage, the following main groups:

1. bone-marrow irritation or stimulation, physical, chemical or allergic

2. liberation leukocytosis, a bone-marrow response to overwhelming demand (hemolysis, anemia)

3. ectopic hematopoiesis secondary to prolonged demand on, or obliteration of, the normal bone marrow.

What has been most difficult to understand, is the occurrence of pronounced reactions in localized carcinoma of parenchymatous organs. Leukemoid reactions have generally been regarded as unusual in clinical practice, but probably occur more often than has been reported in the literature. "In view of the frequent occurrence of conditions that seem adequate to produce them, it is possible that certain persons have inherent predispositions to these reactions, possibly on a familial basis" (5). With regard to primary dermatologic diseases, leukemoid reactions have been described in connection with dermatitis herpetiformis (2), but as far as we have been able to ascertain, never in connection with acne.

It has been demonstrated that, contrary to the conditions in acne vulgaris, patients with conglobate acne have a decreased delayed reactivity to different bacterial and viral antigens. Probably immunologic changes, which are of pathogenetic importance, occur as a result of severe acne (6, 10). This is confirmed by the improvement obtained by corticosteroid therapy in cases "resistant" to antibiotics (3). The mechanism behind the severe, disseminated symptoms in our above-mentioned cases I and II, has been regarded as a type of generalized Arthus reaction (12). This mechanism has also been discussed by Kelly & Burns and by earlier authors (1, 3, 7) in cases of acute toxic acne associated with arthralgia. Consequently, from a pathogenetic point of view, the leukemoid reaction in our cases may be regarded as belonging to the first group in the above classification by Hill & Duncan.

Several of the patients in our material also had pronounced joint symptoms. Two patients suffered from microscopic hematuria, which was interpreted as a sign of focal nephritis. Thus, acute, febrile ulcerative conglobate acne is a syndrome in which the general reaction may be manifested in several different organ systems.

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