

FEBRILE MUCOCUTANEOUS SYNDROMES (ECTODERMOSIS EROSIVA PLURIORIFICIALIS, STEVENS-JOHNSON'S SYNDROME ETC.) IN ADENOVIRUS INFECTIONS

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The febrile mucocutaneous syndrome is a complex of symptoms characterized by fever, exanthema and lesions involving at least two of the body orifices. Many years of study of this syndrome have led the author to the conclusion that it is an allergic reaction (13-17). It can be brought on by certain drugs, as assumed by many authors and as demonstrated in provocation experiments (16). The syndrome has also appeared, however, in conjunction with certain infections for which no drugs were given. Often the combination of infection and drug has a provocative effect. An alimentary cause too, may occasionally be suspected.

Among the infectious causes haemolytic streptococci have a predominant role. Mycoplasma pneumoniae has also proved to be a provocative agent (4, 8, 17). In respect of virus infections the author has seen the syndrome develop in hepatitis, vaccinia and smallpox (18). Herpes simplex may occasionally also be to blame. Mononucleosis infectiosa, in conjunction with which the syndrome is not uncommon, may furthermore be counted among the viral infections.

In the course of the years the means of virological and serological diagnosis have constantly improved and as a result the author believes that the syndrome also may

occur in conjunction with adenoviral infections.

Case histories

1. ♂, 11 years. On Sept. 22, 1959, the patient suffered from headache and had a temperature of 37.8°. On the following day he vomited and had diarrhoea. Sept. 24: photophobia. Sept. 26: afebrile and improved. On Oct. 1 he had a shrimp meal and on the same day developed a rash and started coughing. He was admitted to hospital on Oct. 2. In the mouth red spots were seen on the buccae and petechiae on the palate; furred tongue. Pronounced purulent conjunctivitis. Severe balanitis and reddened urinary meatus. The entire body except the feet was covered with a bright-red, symmetrical maculopapulous rash, partly confluent and of iris type on the thighs. He had fever of at most 38.6°, lasting 3 days. The exanthema persisted for 2 1/2 weeks. Pulmonary X-ray was normal. L.P. normal. Whites 9800 (staff 13, segmented 76, eosinophilic 1, lymphocytic 8, atypical lymphocytes 2 per cent). SR 6-7-10 mm/hour (weekly sample). Electrophoresis: high α_2 and β . Faeces: adenovirus type 7. Complement fixation titre to adenovirus $\geq 64-64$. Provocation test with a shrimp meal was negative both clinically and in thrombocyte reaction.

2. ♂, 20 years. On Jan. 28, 1960, the patient developed a cough which increased and, on Jan. 30, was followed by pharyngeal symptoms and fever of 39.6°. On Feb. 1 he was given a tablet of penicillin V, on Feb. 2 and 3 one tablet 3 times each day. On Feb. 2 he had

swollen lips, smarting eyes, on Feb. 4 a body rash. On admission to hospital he had severe purulent pseudomembranous conjunctivitis, crusts on lips, greyish-white exudate in the entire mouth, petechiae on the palate. Crusts in the nose. Erosions on penis and around anus. On the skin of the trunk and extremities there were relatively sparse bluish-red efflorescences, later purely haemorrhagic, up to a couple of centimetres in size (see Figs. 1-4). Fever varying between 38° and 38.8° lasted for 3 weeks, and the exanthema for 4 weeks. Pulm: rhonchi, X-ray normal. L.P. normal. Whites 6300 (staff 26, segmented 38, eosinophilic 4, lymphocytic 22, atypical lymphocytes 9, monocytic 1 per cent). SR 22-34-46-28 mm/hour. Electrophoresis showed low albumin, elevated α_2 and β globulin. Adenovirus type 7 in faeces. Complement fixation titre to adenovirus 128-128-512. Intracutaneous benzyl penicillin test was negative.

3. ♀, 8 years. Eczema in infancy. Epileptic since 1962, since when she had been treated with Difhydan and barbiturate. On Nov. 21, 1963, she had a score throat and temperature of 39.2°, and was given 1 tablet \times 2 of Sulfadon. On Nov. 22, 1963, her temperature was 39.8° and she had a rash over the entire body. She was admitted to hospital. Ulcerous lips, reddened tonsils, white spots on buccae. Severe conjunctivitis. Ulcerous nostrils and erosions around the anus. The exanthema consisted of bluish-red, symmetrically arranged maculopapules, partly confluent, on trunk and extremities out as far as the hands and feet. The fever, max. 40°, lasted 5 days, the exanthema 2 weeks. Whites 9800 (staff 7, segmented 50, eosinophilic 0, lymphocytic 35, monocytic 8 per cent). Thrombocytes 250,000. S.R. 26-12 mm/hour. Complement fixation titre to adenovirus 64-128-128. No test made for virus in faeces.

4. ♀, 12 years. On Oct. 5, 1963, the patient was tired and had a fever of 37.2°-39°. The fever continued and on Oct. 7 a throat infection was diagnosed. She was given 2 tablets of Sulfadital, and on Oct. 8 another 2 \times 2 tablets. On Oct. 9 she had a rash covering the whole body and was admitted to hospital. She had conjunctivitis and swollen eyelids, dry lips, in the mouth bluish-red spots on the buccal mucosa and abundant small vesicles on the soft palate. Reddened tonsils with small exudates. Round efflorescences about 1/2 cm in size all over the body, densest and confluent on arms and back, circinate on buttocks. Fever of max. 40.1° lasted 9 days. The exanthema disappeared after a few days. Whites 7200 (staff 5,

segmented 55, eosinophilic 0, lymphocytic 26, atypical lymphocytes 4, monocytic 10 per cent). SR 21-3 mm/hour. No test was made for virus in faeces. Complement fixation titre to adenovirus 4-64.

5. ♂, 19 years. Concript, many of whose comrades suffered from upper respiratory infections. He himself contracted a cold and cough on Nov. 17. On Nov. 27 he had a rash on the face and trunk and a sore throat. He had taken no medicine. He was hospitalized on Nov. 28 with a fever of 39.4°, swollen face, moderate conjunctivitis. Orally cavity: reddened rear pharyngeal wall, tonsils reddened with patches of exudate, furred tongue, petechiae on the palate. Maculopapulae of roughly 1/2 cm diameter on the face, throat, trunk and extremities out as far as the palms of the hands, densest on throat and trunk, where they were confluent. Fever of max. 39.4° lasted 6 days. He had then to be discharged to his military unit, the exanthema having almost disappeared. SR 11 mm/hour. Whites 7400 (staff 20, segmented 45, eosinophilic 1, basophilic 1, lymphocytic 28, atypical lymphocytes 5 per cent). Haemolytic streptococci in the pharynx on Nov. 29. Faeces: adenovirus type 7. Complement fixation titre to adenovirus 4. Anti-streptolysin titre 280 units.

6. ♂, 20 years. On March 7, 1965, contracted a cold with fever lasting a few days. The cold returned on March 14 and he was given 2 tablets of penicillin V (taken earlier without reaction). On March 15 he had a temperature of 38.5°-39.6° and a rash on the legs. He was admitted to hospital on the following day. General malaise, 40.5° fever, swollen bleeding lips. Yellowish-white exudate on the whole of the mouth. A severe mucocutaneous syndrome developed, accompanied by purulent membranous conjunctivitis, crusted nostrils and lips, haemorrhagic, membranous stomatitis, severe balanitis with erosions. Rash peripheral on extremities, especially on hands and feet, forearms and legs, with brilliant iris forms, changing to haemorrhagic efflorescences. Fever of max. 40.5° lasted 11 days, the exanthema 3 weeks. L.P. normal. Whites 27,000 (staff 4, segmented 82, eosinophilic 0, lymphocytic 11, monocytic 3 per cent). SR 37-62-30 mm/hour. Electrophoresis: low albumin, high α_2 globulin. Faeces: adenovirus type 7. Complement fixation titre to adenovirus 512-512-256.

Other tests

In cases 1-4 and 6 no pathogenic bacteria were found in nose or pharynx, and no pathological

values or rise of titre existed as regards anti-streptolysin, antistaphylolysin, complement fixation to herpes simplex and influenza or Paul-Bunnell's reaction and cold agglutination. Case 5, on the other hand, had haemolytic streptococci in the pharynx and a high antistreptolysin titre.

Discussion

In comparing the results for the six patients one may discuss in the first place whether general symptoms of acute infection were present. The blood picture showed in five cases normal or low white bloodcell count, leukocytosis being present only in the severest case (no. 6). Shift-to-the-left was marked in four cases, and eosinophilic cells were lacking or sparse in five. The sedimentation rate was slightly to moderately elevated. Electrophoresis, performed in three cases, showed changes of the type associated with acute infection. These findings are consistent with a viral aetiology. By means of a series of bacteriological and serological tests infections of the kinds mentioned as possible causes were excluded in all cases but one (no. 5). The only positive results were related to adenovirus.

What, then, are the findings which suggest the existence of an acute adenoviral infection in these cases? In the first place the clinical prodromal symptoms may be adduced, even if not particularly characteristic in themselves. As a rule the adenoviruses give rise to pharyngeal and upper

respiratory symptoms and, as regards type 7, gastro-intestinal symptoms as well. The diagnosis of acute adenoviral infection should be supported by an, at least, four-fold rise in antibody titre. A high titre, however, should itself be a valuable indication. A certain degree of complement fixation often exists in people at an early age owing to the common occurrence of adenoviral infections, but the C.F. titres are usually low.

To obtain an idea of the titres in cases of febrile mucocutaneous syndrome the other 90 cases have been tabulated in which titres were determined (table 1). In 54 of these cases tests were made for virus in faeces but with negative result. The cases are recorded according to highest titre value.

Table 1. *Complement fixation to adenovirus. Cases unconnected with adenoviral infection*

Highest titre	0	2	4	8	16	32	64
Number of cases	46	4	13	17	8	2	0

In 44 of 90 cases the complement fixation reaction shows that the person had earlier had an adenoviral infection. No infection was present at the time of the examination, as in no case was the rise of titre more than twofold. Tests for virus were made in 28 of the 44 cases but with negative result.

The results for the six patients in the present study are as follows (table 2).

Table 2. *Clinical prodromal symptoms, virus findings and complement fixation titre to adenovirus in six patients*

Case No.	Clinical prodromal symptoms	Virus in faeces	Complement fixation titre			Remarks
			Acute phase	Convalescence phase		
				1	2	
1	Vomiting, diarrhoea; cough	+	≥64	64	—	No drugs. Shrimp meal. Provocation neg.
2	Cough, pharyng. symptoms	+	128	128	512	1 tabl. Pen-V-. Skin test neg.
3	Pharyngeal symptoms	Not tested	64	128	128	Sulfadon, 1 tabl. × 2
4	Pharyngeal symptoms	Not tested	4	64	—	Sulfadital, 2 tabl. × 3
5	Cold, cough	+	4	—	—	No drugs. Streptococcal inf.
6	Cold	+	512	512	256	2 tabl. Pen-V.

The clinical prodromal symptoms, i.e. before the syndrome had developed, are consistent with an adenoviral infection. In case 2 virus was found and the titres were very high and with fourfold rise. In case 4 there was a sixteenfold rise of titre. These two patients had a proved acute adenoviral infection. Patients 1, 3 and 6 had high titres compared with the other patients (table 1), none of whom had a titre of 64. No. 6, in whom virus was found, had a highest titre of 512, and No. 3, for whom no virus test was made, 128. Patient no. 1 had virus in faeces and also a titre of 64. The evidence cannot be considered as definite, but an acute adenoviral infection must be regarded as highly probable in these three cases. In no. 5 virus was found but it was not possible to obtain more than one titre. He may have been a virus carrier.

It is also necessary, for purposes of analysis, to eliminate the effect of other provocative agents, especially drugs administered before the syndrome appeared. Penicillin

V, which had been administered to patients 2 and 6, seldom gives rise to febrile mucocutaneous syndrome, in any case not after single doses (16). The benzyl penicillin test in case no. 2 was also negative. Patients 3 and 4 had been given two respectively three doses of sulph drugs. Here, too, medication usually proceeds the syndrome by several days and long-acting sulph is a particular risk. Some provocative effect in these cases cannot be altogether eliminated. Patients 1 and 5 had been given no medicine. The possibility of an alimentary cause in case no. 1 as a result of eating shrimps is contradicted by the negative provocation test.

As regards the types of mucocutaneous reaction these are shown in table 3. Some reservation must be made in respect of conjunctivitis, since this is often brought on by adenovirus, but not in the severe purulent or pseudomembranous form found in several of these cases.

Table 3. Types of mucocutaneous syndrome

Case	Lesions of skin and mucosa						Remarks
	Skin	Eyes	Nose	Mouth	Gen.	Anus	
1	+	+	-	+	+	-	
2	+	+	+	+	+	+	Ectod. eros. pluriorif.
3	+	+	+	+	-	+	
4	+	+	-	+	-	-	Stevens-Johnson's syndrome
5	+	+	-	+	-	-	Stevens-Johnson's syndrome
6	+	+	+	+	+	-	

The mildest forms occurred in cases 4 and 5, in which skin, conjunctiva and oral cavity alone were effected. The skin displayed generally maculous exanthema over the greater part of the body, the conjunctivae were moderately inflamed and the oral cavity showed enanthema, small vesicles or petechiae in the palate. These cases represent what was originally meant by a Stevens-Johnson's syndrome of relatively mild type. In the other cases the skin lesions were of a more intense character, maculopapulous, bright-red in colour, and in two cases of partially iris type. The con-

junctivitis was more severe and even purulently pseudomembranous; the same applied to the stomatitis, in addition to which there were scabs in the nose and inflammation and erosions on the genitals and around the anus. In case no. 2 all orifices were attacked; this represented a case of the total syndrome, as first described by Rendu (11) and later on by Fiessinger *et al.* (3) and was then called Ectodermosis erosiva pluriorificialis.

These and many other special appellations have hardly any justification (16). Many variations occur as regards combina-

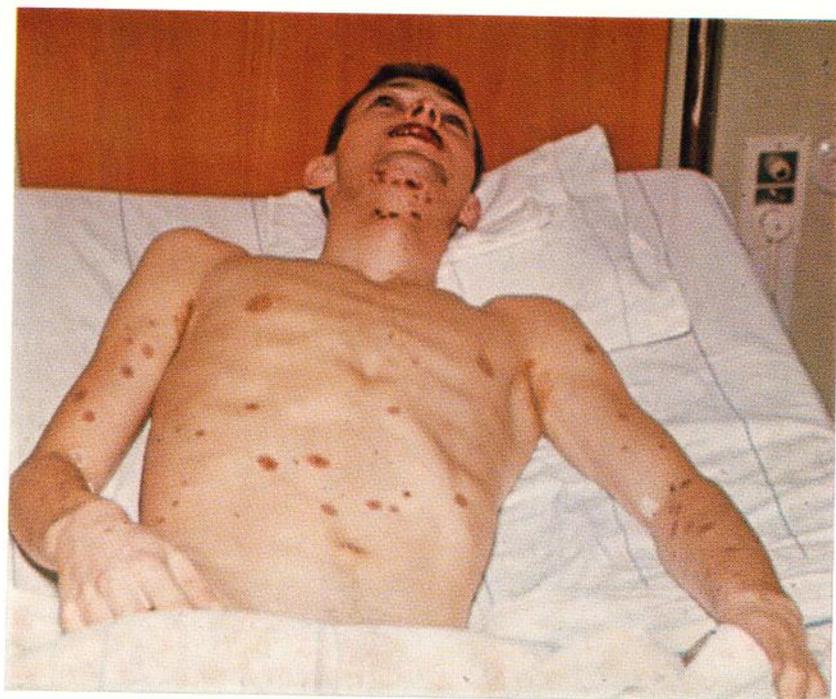


Fig. 1. Case 2. Haemorrhagic exanthema.

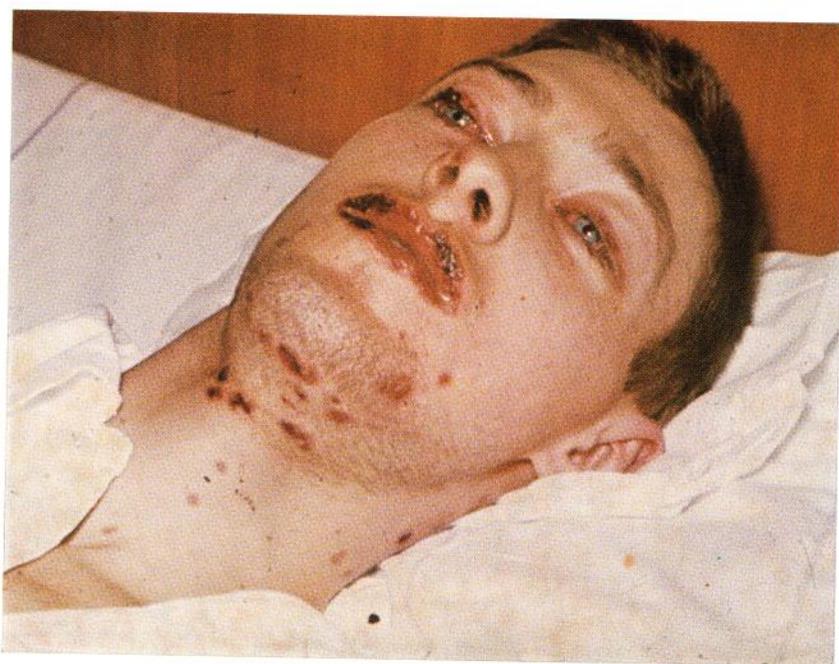


Fig. 2. Case 2. Conjunctivitis. Crusts on lips and in the nose.



Fig. 3. Case 2. Erosion on penis.



Fig. 4. Case 2. Erosions around anus.

tions of exanthema of different types and affections of one or more orifices. In the author's series of more than 200 cases 16 variants have been seen so far. The present six cases represent five different types.

Fever, often high and of long duration, is inherently a component of the "febrile mucocutaneous syndrome". In the present cases it reached 38.6° to 40.5° and lasted from 3 days to 3 weeks. Quite naturally, however, in these cases the fever may be caused to some extent by the infection.

A priori it may seem surprising to find that adenovirus can give rise to this allergic reaction. In other provocative infections such as streptococci, mycoplasma, vaccinia, variola, hepatitis and mononucleosis allergic reactions in the form of different types of exanthema are not altogether uncommon, and this may indicate some disposition to allergic manifestations, the most severe form of which is the mucocutaneous syndrome. However, careful study of the adenovirus literature shows that many authors in describing adenovirus infections have observed exanthema of uncharacteristic, rubeoliform or morbilliform type, including conditions resembling exanthema subitum (1, 2, 5, 6, 7, 9, 10, 12). According to one observation (6) exanthema occurred in conjunction with viraemia caused by adenovirus 4 and 7.

SUMMARY

In 6 out of 96 patients with a febrile mucocutaneous syndrome some relation with adenoviral infection is reported. Cultures harboured adenovirus type 7 in faeces of four patients. Serologically two cases could be definitely and three cases in all probability established as acute adenoviral infections. The sixth patient had a double infection with haemolytic streptococci.

In the five patients with acute adenoviral infection bacteriological and serological tests showed no other provocative infection which might be associated with mucocutaneous syndrome. Likewise the effect of drugs given in certain cases or of alimentary factors could in all probability be excluded.

The five patients represented as many clinical forms of mucocutaneous syndrome, varying in severity from the mildest (Stevens-Johnson's syndrome) to the most serious (Ectodermosis erosiva pluriorificialis).

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