THE JOURNAL OF INVESTIGATIVE DERMATOLOGY VOL. 43, NO. 2

Printed in U.S.A.

A RELATIONSHIP BETWEEN ERYTHEMA MULTIFORME AND HISTOPLASMOSIS*

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Erythema multiforme is a clinical syndrome of uncertain etiology. Some cases have been associated with tuberculosis (1), other bacterial or viral infection (2), or with drug sensitivity reactions (2). Whereas erythema nodosum occurs in patients with acute histoplasmosis (3), the association of erythema multiforme with *H. capsulatum* infection has not been previously recognized.

In the six week period during September and October 1963, eleven patients with erythema multiforme were seen. Each case fulfilled the classical criteria for this diagnosis, demonstrating multiform erythematous bullous and vesicular lesions on the face, body and limbs. Many of the lesions evolved into the "target" pattern and in some there were hemorrhagic changes (Fig. 1). Some of the lesions on the limbs were deeper and indurated. Nine of these patients had severe influenza-like symptoms with cough, fever up to 104° F., malaise, myalgia and arthralgia. The other two had no constitutional symptoms. One patient had been receiving diphenylhydantoin, and another chlorpropamide, but the remaining nine had received no drugs.

Because of the coincidence of the severe constitutional symptoms and the time of occurrence (seven cases in one week; six were in hospital at the same time) a common viral etiology was sought. Blood was therefore drawn from four patients for virus antibody titre determinations. The serum was frozen until the convalescent blood specimens for the necessary comparison could be drawn. This convalescent sample was not drawn, however, until much later ("vide infra").

In November and December 1963, this hospital and other hospitals in this city became aware of an unprecedented number of cases of histoplasmosis—acute, subacute and disseminated (4). The history revealed that in many patients the illness began in September or October 1963 with an acute influenza-like illness characterized by cough, fever, malaise, myalgia and arthralgia which is compatible with a diagnosis of acute histoplasmosis (5). Several patients had lesions of erythema nodosum. Because the patients with histoplasmosis and the above-mentioned patients with erythema multiforme had such similar constitutional symptoms and were ill during the same time period, it was decided to recall the eleven patients and test them for evidence of recent infection with *H. capsulatum*. This was done in January 1964. Thus three months had elapsed from the time of the acute illness. Each patient was questioned about exposure to possible sources of *H. capsulatum* (contact with chickens, pigeons or construction sites). A sample of blood was taken from each, and then histoplasmin skin tests were performed by injecting 0.1 cc histoplasmin (Parke Davis) into the volar surface of the forearm. An area of erythema and induration 0.7 cm in diameter or greater at 48 hours was considered a positive reaction. Three or these patients were also tested with PPD, intermediate strength.

The four acute phase sera and the eleven "convalescent" sera taken in January 1964 were sent to the Ontario Department of Health, Division of Laboratories, Toronto, to be tested for complement fixing antibodies for antigens of *histoplasma capsulatum* (yeast phase and mycelial phase).

A control group of 200 healthy people were tested to determine the expected incidence of skin reactors to histoplasmin in the normal population.

RESULTS

The incidence of reactors in the normal group tested was 25% (50 of 200). The incidence in people under 40 years of age was 34%, while in those over 40 it was 20%. There was no sex difference. This apparent discrepancy can be explained by the fact that most people over 40 in this hospital are European immigrants as are 10 of the 11 patients with erythema multiforme. Most of those under 40 are native-born Montrealers. The intensity of the reactions

Received for publication July 25, 1964.
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varied from minimal (slight induration and erythema 0.7 cm in diameter) to severe (an area of erythema and induration 4 cm in diameter—but with no necrosis).

The 11 cases of erythema multiforme are summarized in Table I. Each of these patients reacted positively to the histoplasmin skin test and in every case the reaction was severe. The 3 patients skin tested with PPD did not react to it. In 3 of the 4 cases in which an acute phase serum and a three month convalescent serum was drawn there was a changing titre of complement fixing antibodies for yeast phase *H. capsulatum* antigens. In one of the other cases the *H. capsulatum* antibody titre was 1:32 which is diagnostic of recent or active

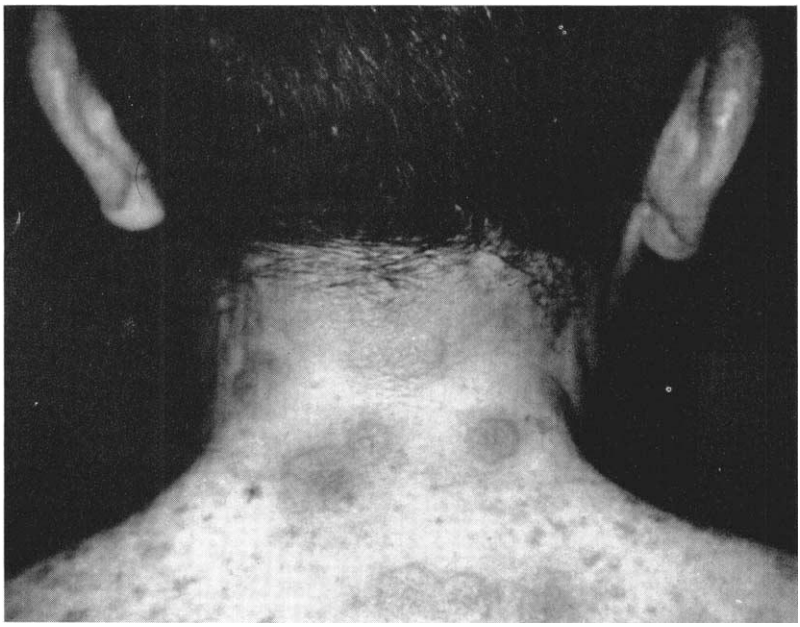

FIG. 1. Typical erythema multiforme lesions in case #5. The lesions resolved spontaneously in three weeks.

TABLE I

Clinical data on patients with erythema multiforme

Case No.	Age	Sex	PPD Intermed. Strength	Histoplasmin Skin Test	CF Antibody Titre Acute Phase	CF Antibody Titre 3 Months	Flu-like Illness	Remarks
1	40	F		Severe	1/4	1/16	+	Receiving diphenylhydantoin before and after.
2	67	F		Severe	1/64	1/16	+	Receiving chlorpropamide.
3	55	F		Severe	1/4	1/8	+	
4	42	F		Severe	0	0	+	
5	46	M		Severe	—	1/32	+	Also has Marie Strumpell ankylosing spondylitis.
6	50	F		Severe		1/16	+	Parakeet in the house.
7	58	F		Severe		0		
8	51	F		Severe		0	+	Illness developed while on chicken farm.
9	48	F	—	Severe		0	+	
10	68	F	—	Severe		1/8	−	
11	50	F	—	Severe		0	−	

infection with *H. capsulatum* (6), while a lower titre was present in 2 additional cases.

In one patient erythema multiforme with constitutional symptoms began seven days after visiting a chicken farm, a classical source of *H. capsulatum*.

Ten of the eleven patients were women and all were over 40 years of age.

DISCUSSION

The present study indicates both statistically and directly that in at least some of the 11 cases reported, erythema multiforme was a manifestation of acute infection with *H. capsulatum*.

In Montreal where the skin test reaction rate to histoplasmin is 25%, the probability that 11 consecutive cases of erythema multiforme would react to histoplasmin is about one in four million if there were no relationship between these two conditions. Thus on the basis of the skin tests alone, the relationship between these two diseases is practically certain. The serological studies in several patients provide more specific evidence of the above relationship. In case *2* the change in titre of complement fixing antibodies to yeast phase antigens of *H. capsulatum* from 1:64 (acute phase) to 1:16 (3 month convalescent phase) establishes that an infection with *H. capsulatum* had occurred at this time. Since the constitutional symptoms associated with erythema multiforme were typical of acute histoplasmosis, since the time of the patient's illness coincided with an outbreak of histoplasmosis, and since the patient had no other disease in the time interval under study, we must conclude that in this case erythema multiforme was a manifestation of histoplasmosis. In case *5* the evidence is almost as conclusive even though an acute phase serum was not studied.

In acute histoplasmosis the complement-fixing antibody titre may rise from 0 to 256 and fall back to zero in 75 days (7). Thus a change in titre in 3 months such as occurred in cases *1* and *3*, though not diagnostic of acute histoplasma infection is suggestive of this diagnosis, especially in view of the coincidence of clinical and epidemiological factors. The same can be said of the lower 3 month antibody titres in cases *6* and *10*. The negative early and late antibody titres in case *4*, and the negative late titres in cases *7*, *8*, *9* and *11* do not exclude the possibility that they had acute histoplasmosis in October 1963. It is apparent, however, that not every case of erythema multiforme in this series was necessarily due to histoplasmosis.

In contrast to most of the other patients with acute histoplasmosis seen in the autumn of 1963—in whom malaise, cough and pulmonary infiltrates persisted for several months—all of the patients with erythema multiforme were well within one month and none showed pulmonary lesions on X-ray. Another feature was the very marked skin reactivity to histoplasmin of the erythema multiforme group. An hypothesis that these patients developed erythema multiforme as a manifestation of marked hypersensitivity and immunity to *H. capsulatum* would explain their violent acute illness, their marked skin reactivity and their rapid recovery, as well as the relatively low 3 month complement fixing antibody titres in many cases.

It may be argued that the skin reactivity to histoplasmin was a consequence of the erythema multiforme syndrome. However, since all the patients were tested 3 months after complete recovery, and because in the three cases so tested the skin reactions to PPD, intermediate strength, were negative, this contrary thesis is extremely unlikely.

SUMMARY

In September and October of 1963 eleven patients presented with erythema multiforme, nine of whom had severe constitutional symptoms. This coincided with an outbreak of histoplasmosis in the community. In each patient a positive histoplasmin skin test was elicited and in several cases serological evidence of acute histoplasmosis was demonstrated. This and other evidence make it seem likely that acute histoplasmosis can be a cause of erythema multiforme.

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