On the "Yatobyō" Exanthem (Tularemid)

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(Received for publication, August 28, 1953)

The first clinical and epidemiological description of the disease called tularemia in modern times was made in our country in 1837 by a surgeon, Homma Soken, who was a court physician of a feudal lord of Mito district. He described this disease as "hare meat poisoning" in his textbook of surgery, Vol. 9 (Yoka-Hiroku).

In 1924 H. Ohara¹⁾ reported for the first time in Japan scientifically on the same disease as an acute febrile disease caused by a microbe transmitted by wild rabbit. He called this disease "Yatobyō" and named the causative organism Ohara-Haga Coccus, later "Yatobyō" Bacteria.

The identity of the "Yatobyō" with tularemia, as he had anticipated, was proved in 1925 by Francis and Moore,²⁾ who called "Yatobyō" (tularemia in Japan) Ohara's disease, because the studies of this disease in both countries were done independently.

The exanthem which occurs in the course of tularemia was described by Francis, Parker & Spencer, Hitch & Smith,³⁾ Pullen & Stuart⁴⁾ and many other authors, while in Japan the exanthem which was noted by "Yatobyō" was reported only by H. Ohara in 1926 and by I. Ota⁵⁾ in 1936. Report on this case was also published by Prof. M. Ota.

Case Reports

We report here 9 instances (Table I) exhibiting the so-called "Yatobyō" exanthem among 230 cases of Yatobyō which were treated at Ohara General Hospital during the last sixteen years from Jan. 1937.

Frequency of the exanthem: According to H. Ohara, it was noted in 17 out of 239 cases (7.1%) from 1929 to 1939, and M. Sato,⁶⁾ one of the authors, observed in 7 out of 180 cases (3.9%) from 1940 to 1952 in Ohara General Hospital; Maeda (1952) reported 4 out of 33 cases (12%) at Chiba prefecture, while Miwa *et al.*⁷⁾ noted, in the same epidemic, 4 out of 10 cases (40%).

On the other hand, in America, Francis noted it in 32 out of 679 cases of tularemia (4.7%, 1928); Pullen & Stuart, in 19 out of 225 cases

(8.44%, 1944); Simpson, in 5% (1929); Kavanaugh, in 23 out of 123 cases (18.7%, 1935); Arzt, in 3 out of 15 cases (20%, 1938); Foshay, in 120 out of 600 cases (20%, 1940); Rabe & Cruse, 2 out of 81 cases (2.5%, 1950-52). H. Reich described recently that there were only two cases with exanthem out of 135 tularemia which broke out in the Turkish army at Garrison Lüleburgaz. Thus about the frequency of skin eruption of this disease the authors differ from each other in their estimations.

Sex, age and occupation: Among the nine cases we observed, six were male and three female. Their ages ranged from 22 to 59 years.

The occupation of seven among them were farming. In short, "Yatobyō" patients with exanthem reported here were mostly young male farmers, who had frequent opportunities of contact with wild rabbits and had little knowledge concerning the subject disease.

Seasonal incidence: These patients appeared chiefly in winter, seven cases in the period of October to next February, three cases of them occurred in December and the other two cases in May and July, respectively.

Most patients were infected by wild rabbits, but only one case (No. VII), which occurred in July, was caused by tick-bite on the scrotum. It responded to the seasonal incidence of all "Yatobyō" patients, of which the highest incidence occurred in the hunting season with the next greatest frequency in late spring.

Clinical classification: When these instances were classified into clinical types, the ulceroglandular type was found in four, the glandular in three, the oculoglandular and the typhoidal types in one case each. As Hitch & Smith have reported concerning tularemia, we did not observe any relation between the appearance of exanthem and the clinical cause of the disease either.

Duration from onset to eruption: The eruption appeared at the same time with the onset of the illness in some cases (No. II and IV), but it appeared commonly in the first or the second week of illness. H. Ohara or Maeda said that it appeared mainly in seven to ten days from the onset; Miwa and his co-workers said that it appeared mostly during the second week of illness.

On the other hand, Hitch & Smith reported that tularemic eruption of 29 cases appeared mostly during the second or the third week in average on the 16th day of illness. The authors reported that the shortest time which elapsed before appearance of the eruption was five days (Kerlin's case), while the longest was three months (Corn's case). Kavanaugh reported of 23 cases, and Pullen & Stuart of 15 cases, that it appeared chiefly in the second or the third week of illness.

Distribution of exanthem: This exanthem was usually noted on the

Fig. 1

Fig. 2

Fig. 1. Case VI, Erythema multiforme on neck.

Fig. 2. Case VIII, Adenopathy in left axilla, before the operation.

Fig. 3

Fig. 4

Fig. 3. Extracted pathologic lymphnodes of case VIII.

Fig. 4. A week after the operation of case VIII.

upper trunk, namely on the face, the neck (Fig. I), the breast, the shoulders, the upper extremities or the hands and it was more frequently noted on the left side than on the right.

An interesting fact is that the exanthem was frequently localized on the same side as the adenopathy. But Miwa reported that it was noted

TABLE
Summary List of Cases of

No.	Sex.	Age	Occupation	Time of onset of illness (Month)	Type of illness	Portion of primary lesion	Days from onset to eruption
I	♀	36	farmer's wife	November	U. G.*	left fore-finger	5
II	♂	58	farmer	December	O. G.**	both eyes	at the same time
III	♀	59	farmer's wife	February	G.***		7
IV	♂	34	farmer	November	G.		at the same time
V	♂	34	farmer	December	U. G.	right third finger	10
VI	♂	35	labourer	May	G.		2
VII	♂	43	office worker	July	U. G.	left half of scrotum	14
VIII	♂	22	farmer	October	U. G.	left thumb	20
IX	♀	27	farmer's wife	December	Typhoidal		3

* Ulceroglandular, ** Oculoglandular, *** Glandular.

most frequently on the lower extremities and next on the forearms, the upper arms, the thigh, the forehead, the neck, the breast and the back of the body.

Hitch & Smith reported that although the eruption might be generalized or involves any one or several regions of the body, most patients had it on the upper portion of the trunk and the upper extremities, and in some instances the eruption was unilateral or at least more marked on one side. And they said that almost invariably this was the side on which the primary lesion occurred, and most patients with tularemia of the primary ophthalmic type presented a facial eruption, which was occasionally unilateral. Kavanaugh and Pullen & Stuart described that it was noted most commonly on the upper extremities, the hands or the neck on one or both sides.

Types of Eruption: The eruption was various in type and not specific; sometimes of erythema multiforme or erythema nodosum type, at others urticarial, erythematous or follicular and resembling acne vulgaris. Usually the eruption accompanied a slightly itchy or a painful feeling.

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"Yatoby" Exanthems

Distribution of eruption	Type of eruption	Duration of eruption (days)	Skin test (mm) 24 hours (48 hours)	Agglutination	Slide agglutination (seconds)	Bacterial culture
face, neck, breast, left hand	erythema multiforme	14	strongly positive	640×	2	(+)
neck, shoulder, left forearm, hands	erythematous	13	20×20	1280×	3	
left face	acne vulgaris		strongly positive	320×	32	
all over the body	urticarial	several days				(+)
neck, breast	follicular	16	23×25	320×	10	
left face, left neck	erythema multiforme	28	27×30 (35×40)	1280×	5	(+)
left neck, back, hands	erythema multiforme	14	15×16 (12×15)	20×640×	70 5	(+)
face	acne vulgaris	12	35×40	1280×	5	(+)
upper and lower extremities	erythema annulare, erythema nodosum	24	20×13	80×160×	15	(+)

It had occasionally inflammatory nature. Three cases reported by Foshay, two cases each by Hüseyin & Kemal and Arzt, and one case each by Francis, Hitch & Smith, Berde, Netousék, Ebert and Balluch were erythema multiforme. Arzt noted one case of ecthymata, which appeared on the gluteal and the genital regions. Six cases each reported by Foshay and Pullen & Stuart, two each by Kavanaugh and Miwa, one each by Kerl and Foerster, were all of erythema nodosum type. Konrad reported one case of erythema scarlatiniforme type. Two cases reported by Ledingham & Fraser had acne vulgaris-like eruption on the back, one case by Simpson had it on the neck too, more than 17 cases by Pullen & Stuart had herpes labialis type, and Francis described one case of "extreme herpes."

The original cause of these eruptions was, as H. Ohara and I. Ota reported concerning the first case of our collections, presumed to be allergic in nature. It was presumed that the eruption was of septic-pyemic nature, which occurred as a result of lymphatic and hematogenic spreading of bacterial toxic factors.

Duration of the eruption: The average duration of the eruption was

19.5 days; mostly it disappeared leaving no trace in one or two weeks after extirpation of the pathologic lymph nodes (Fig. 2, 3 and 4) and in four cases after injection of 0.5 g. of streptomycin every day (No. VI, VII, VIII and IX). Only one case, No. VII, showed pigmentation after the disappearance of the eruption.

Miwa reported that the eruption disappeared in 3 to 7 weeks after the appearance. Hitch & Smith reported that the shortest duration of the eruption was two days, while the longest was in a case reported by Mc Gray, in which there were recurrent manifestations for over 113 days, and the average duration of the eruption was twenty one and nine tenths days.

As our report showed, Pullen & Stuart also described the eruption as persisting for several days to about three weeks. But they described that doubt existed as to the etiology of the four patients in erythema nodosum type, because sulfonamides were being administered when the skin manifestations first became apparent, and in each of these cases the skin eruption subsided within four days after the sulfonamides administration was discontinued.

Specific examinations: 1) Intradermal test. This examination is the most reliable diagnostic method for this disease, the reaction occurring in a specific manner in two or three days after the onset of the illness. Wherry advocated at first this specific reaction in 1917 and later in 1932 Foshay³⁾ made bacterial protein antigen for this skin test for tularemia, while in Japan H. Ohara, Kobayashi, Hiwatashi and T. Ota reported the skin test for "Yatobyu," in which bacterial suspension was used as antigen.

We made an antigen by the following method: A 0.01% bacterial suspension of heat-killed bacterium tularensis was made from Ebina strain, to which 0.5% carbol was added. 0.1 cc. of this fluid was injected intradermally in the forearm. This test was done in 8 out of 9 cases here reported, all of which showed extreme positive reaction; the local portion became reddish and showed swelling in the size of 2 to 4 or 5 cm. in diameter 12 hours after the injection. After 24 hours it became edematous and blistered and was accompanied by a slight pain or a fairly itchy feeling, but after 72 hours the lesions began to fade slowly and pigmentation was left at the spot of injection.

2) Serum-agglutination. A specific agglutinin is produced in the serum of "Yatobyu" patients, and so serum agglutination too is useful, but it usually becomes positive after eight or ten days, sometimes in the second week of the illness. So this test can not be used as a method of early diagnosis. The titre rises generally to the highest level in the 3rd or 4th week, thereafter it falls down gradually and the agglutinin of lower

titre persists for the length of about twenty or thirty years. We made a formolized (0.5%) suspension of *bact. tularensis* (5 mg/cc), by which eight out of nine cases reported here were tested for agglutination. Case VII showed a level of 1:20 on the 11th day, case IV showed a level of 1:80 on the 12th day of illness and the titre of the later case rose on to 1:1280 after about a month.

3) Slide agglutination. A drop of the serum of hemolyzed blood of the patient was put on a slide glass, to which a drop of the bacterial suspension was mixed and then the agglutination, which might occur within about a minute, was examined. We tested all cases and the average time of slide agglutinations was 18 seconds. A case, in which this test occurred in 70 seconds on the 11th day of the illness, showed positive result in 5 seconds after about a month (case VII).

SUMMARY

Nine cases exhibiting cutaneous eruptions among 230 cases of "Yatoby" (Tularemia in Japan) at Ohara General Hospital during the last sixteen years from Jan., 1937 to Dec., 1952 were studied.

Most of them were young farmers (6 male and 3 female) from 20 to 30 years of age, who had many chances of contact with wild rabbits in the hunting season, (from November to next February), but only one case, which occurred in July, was caused by tick-bite on the scrotum.

The eruption developed chiefly during the first or second week of the illness, but in two cases, it developed at the same time with the onset of the disease. The sites of predilection are the face, the neck, the breast and the upper extremities, i.e. parts in the upper half of the body. Moreover, it is an interesting fact that the exanthem was frequently localized at the same side as the adenopathy.

The eruption was various in type and not specific; sometimes of erythema multiforme or erythema nodosum type, at others urticarial, erythematous or follicular and resembling acne vulgaris. Usually the eruption accompanied fairly itchy or painful feelings.

It seemed to be an allergic exanthem, which disappeared with no trace in two or three weeks.

The skin test by heat-killed bacterial suspension was positive in eight cases, and the serum- and slide agglutination tests were positive in all cases. The antigen used was made from *bact. tularensis*, Ebina strain, which was isolated from "Yatoby" patients in our laboratory.

We express our deepest gratitude to Dr. Minor Itô, Professor of Tohoku University, for kindly revising this report, and to Dr. S. Ohara, Director of Ohara General Hospital, for his guidance in preparing it.

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