ABNORMAL CUTANEOUS RESPONSE TO MOSQUITO BITES IN CANCER PATIENTS

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Summary

A skin eruption simulating 'papular urticaria' was observed in 6% of 500 patients with cancer. Twenty seven of them had carcinoma affecting different organs, while 3 had lymphoma. Direct observation revealed that the skin lesions were the result of bites by the mosquitoes. There was direct correlation between mosquito bite reaction and the response to intradermal tests with mosquito salivary antigen (MSA). The leucocyte migration inhibition test using MSA revealed the existence of cell mediated immunity to MSA in these patients with 'papular urticaria'. Specific treatment for malignancy apparently influenced the pattern of reaction to ID test as well as to mosquito bites. The histopathologic studies revealed non specific changes in the delayed papules after mosquito bites. The MSA test papules closely simulated morphologically and histologically, the delayed papules of mosquito bites. None of the 12 attendants of cancer patients who were exposed to similar environment as that of patient, while in the ward or at home, developed similar reaction either to MSA or to direct mosquito bite. None of the healthy volunteers or patients with diseases other than cancer, developed similar reaction either to MSA or to direct bites by mosquitoes. The role of irradiation and malignancy in the abolition of "Suppressor T cell" activity in the aetiology of these skin eruptions is discussed.

KEY WORDS: Mosquito bite, papular urticaria, delayed response to mosquito bites, salivary antigen mosquito, Leucocyte migration inhibition test, histology – mosquito bites, suppressor T cells, intradermal test – mosquito antigen.

A peculiar skin eruption characterised by discrete papules and papulo vesicles with or without urticarial bases and central haemorrhagic puncta were seen in adult cancer patients admitted to the Medical College Hospital, Calicut. The skin lesions were on uncovered areas of the body, intensely pruritic and morphologically similar to the 'papular urticaria' of early childhood. Mosquito bites constitute the commonest cause of 'papular urticaria' in this area. Although mosquitoes are prevalent in and around the hospital and it can safely be presumed that all patients in the hospital are bitten by mosquitoes, only cancer patients showed the abnormal response

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to their bites. Patients admitted in other wards of the hospital with diseases other than cancer did not show such a response to mosquito bites. So it was presumed that cancer per se and or anticancer therapy was responsible for such an abnormal response. Curiously enough, there seems to be only scanty references in medical literature to this inter-relationship between cancer and abnormal response to mosquito bites. An attempt is made to study this problem in depth and to delineate the causal factors of these eruptions.

Review of the Literature

Patients with malignancy are known to react abnormally to many antigens producing delayed hypersensitivity response. Anergy often occurs to such antigens as PPD [1,2]. But exaggeration of delayed response to mosquito bites in association with chronic lymphatic leukemia has also been reported[3]. Houston and Keene[4] also observed a similar phenomenon in a patient with lymphatic leukemia. Such a response to mosquito bites has been mentioned as a sign of internal malignancy[5]. The antigenic material present in the saliva of the mosquitoes causes allergic responses in the skin [6,7]. The sequence of events occurring after repeated bites by mosquitoes in man can be summarised into five stages[5,6] - 1, No response 2, delayed response 3, delayed and immediate response 4, Immediate response alone 5, No response (tolerance). Most adults react to mosquito bites by either mild urticarial reaction or no reaction at all. Spontaneous development of delayed hypersensitivity response to mosquito bites is exceedingly rare in individuals past middle age[9] and if it occurs it implies loss of acquired desensitisation.

The cutaneous lesions at various stages of desensitisation to mosquito bites are different. The delayed reaction which takes about 48 hrs. to develop is characteristically an indurated raised itchy papule. The reaction is brought about by specifically sensitized lymphocytes in contact with antigen as a result of which macrophages are activated and a typical histological picture of mononuclear cell infiltration appears. Many biologically active substances are released by sensitised lymphocytes during this reaction. The development of an immediate response together with a delayed reaction represents an intermediate stage of desensitization. Still later stage of sensitisation is characterised by an immediate reaction alone which occurs within half an hour after the bite and consists of a soft wheal[10].

Papular urticaria represents the earliest (tuberculin) allergic phase in the development cycle of insect allergy. It is a common and troublesome skin disease of early childhood. The clinical, histological, immunological, epidemiologic and therapeutic aspects support the parasitic origin of papular urticaria. Clinically, the biphasic course of lesions of papular urticaria – a wheal followed by a papule – is characteristic of insect bite reaction. Shaffer et al[11] observed close histologic similarity of the lesions of papular urticaria, insect bites and test sites of the skin challenged with insect antigen.

Materials and Methods

All patients admitted for the treatment of malignancy either in the medical or in the cancer wards of the Medical College Hospital, Calicut from Feb. 1977 to June 1978 were included in this study. They were kept under close observation from the date of their admission for evidence of insect bite reactions. Those who developed pruritic papules, with central haemorrhagic puncta on uncovered areas of the body were presumed to be suffering from insect bite reaction and were subjected to detailed study. After recording the relevant personal data, each patient was questioned in detail

regarding personal and family history of allergy with special reference to atopy and nature of response to mosquito bites prior to the onset of present illness. The sites and nature of the skin lesions were recorded. The total and differential leucocyte count, haemoglobin estimation and urine analysis were done in all patients.

Special Investigations

A. Intra dermal (I.D.) test with Mosquito salivary antigen (MSA) : *preparation of the antigen :-* The mosquitoes were identified from a sampling of them collected from different parts of the hospital including the cancer wards. A total of 400 mosquitoes were used for this, among which 98% belonged to culex species. Only female culex mosquitoes were used for preparing MSA. The salivary glands were dissected out from these 400 mosquitoes by a modified Hudson et al[12] method. Antigen was prepared by a modified Evelyn et al[13] method.

Fifteen ml of N. Saline was added to the salivary glands dissected out from 400 female culex mosquitoes and this mixture was ground in a ball mill for one hour and kept for 24 hours in cold with intermittent shaking. The mixture was then filtered and pH of the solution was adjusted to 7. It was then filtered through a millipore filter. This was subjected to culture tests for ensuring bacteriological sterility. Standardization of the antigen was done by Turbidimetri method[14] and the concentration of the protein was adjusted to 10 mg/100 ml. This antigen was then stored frozen in refrigerator and was used for the tests.

ID Test : 0.1 ml (10 micro gram) of the antigen (MSA) was injected intradermally on one forearm and as control, 0.1 ml of 0.9 molar sodium chloride was injected ID into the opposite forearm. The following groups were subjected to ID tests with MSA. Group I. All cancer patients who showed abnormal response to mosquito bites during or after receiving a course of chemo and or radiotherapy. Group II : Fifteen healthy human Volunteers. Group III : Fifteen patients admitted in general medical wards with diseases other than cancer. Group IV : 25 cancer patients on the day of their admission to cancer wards awaiting therapy. Group V : 15 cancer patients belonging to Group IV after getting a course of chemo and or radiotherapy and who did not show abnormal response to mosquito bites prior to or during therapy. The test sites were closely observed for 72 hours. The wheal and flare response of more than 5 mm and indurated papules of more than 5 mm were taken as positive immediate and delayed reactions respectively to the test antigen.

B. Mosquito bites – direct observation : The sequence of the changes following mosquito bites in premarked sites were observed directly in all the 5 groups.

C. Leucocyte migration inhibition (LMI) tests : The ability of the MSA to inhibit the migration of leucocytes from 10 cancer patients who showed abnormal response to mosquito bites and from 5 healthy human volunteers, as control, was noted in vitro, by a modified method described by George and Vaughan[15]. The area of migration of leucocytes in the chamber was traced on a paper using Leitz projection and quantitated plani-metrically. From the average of four migration areas of test cultures and controls, a migration index was calculated using the formula[16]:

$$MI - \frac{\text{Migration in presence of antigen}}{\text{Migration in medium alone}}$$

D. Histological studies from :

1. Skin lesions from sites of exaggerated response to mosquito bites from 18 cancer patients.
2. Five positive test sites after MSA ID tests.

E. Patient's attendants were also examined while in the ward for evidence of abnormal reaction to mosquito bites. The relationship of these people to the patients, their residence and previous response to mosquito bites if any were also recorded.

Observations

Among the 500 cancer patients 30 (6%) developed abnormal response to mosquito bites. The cutaneous lesions simulated papular urticaria of early childhood. The male to female ratio was 1 : 9 and the majority belonged to the age group in this area. The youngest patient was 16 years old and the oldest was 68 years. Twenty seven of the patients had carcinoma affecting different organs while 3 had lymphoma. Carcinoma of the breasts and cervix uteri were the commonest (Table 1). Twenty patients received irradiation alone and others had both chemo and radio - therapy. Only two patients had family history of atopy. None of the 12 attendants of cancer patients who were exposed to the same environment as that of the patients while in the ward or at home developed abnormal response to mosquito bites. Haemogram revealed eosinophilia in 19 patients.

TABLE 1

Types of Malignancy in Patients.

Serial No.	Types of malignancy	No. of patients	% of total
1.	Carcinoma breast	9	30
2.	Carcinoma cervix	9	30
3.	Carcinoma pharynx	2	6.7
4.	Carcinoma oesophagus	2	6.7
5.	Carcinoma ovary	1	3.3
6.	Carcinoma bronchus	1	3.3
7.	Carcinoma alveolus	1	3.3
8.	Carcinoma cheek	1	3.3
9.	Carcinoma thyroid	1	3.3
10.	Hodgkin's disease	2	6 7
11.	Lymphocytic lymphoma	1	3.4
	Total	30	100

All thirty patients developed well circumscribed discrete bilateral indurated papules 4–10 mm in diameter, with central haemorrhagic puncta. Lesions were strictly confined to the uncovered areas of the body (Figs. 1 and 2). The result of the MSA intradermal test in various groups are given in Table 2.

Mosquito bite response

Direct observation : The results in various groups are given in Table 3. *Leucocyte migration inhibition (LMI test)*: Significant inhibition of migration of the leucocytes was noted in 6 of the 10 test chambers. The percentage of inhibition varied from 44 to 83%. Similar tests with leucocytes from 5 healthy volunteers showed only insignificant inhibition of migration (Table 4 a, b) ; (Fig 3.)

TABLE 2

Mosquito salivary antigen I. D. test results in various groups

Sl. No.	Type of reaction	Mosquito Salivary antigen I. D. Test				
		Group I 30 cases	Group II 15 cases	Group III 15 cases	Group IV 25 cases	Group V 15 cases
1	Immediate and delayed positive	15	Nil	Nil	Nil	2
2	Immediate positive delayed negative	6	8	6	18	13
3	Immediate negative delayed positive	2	Nil	Nil	Nil	Nil
4	No reaction	7	7	9	7	Nil
	Total	30	15	15	25	15

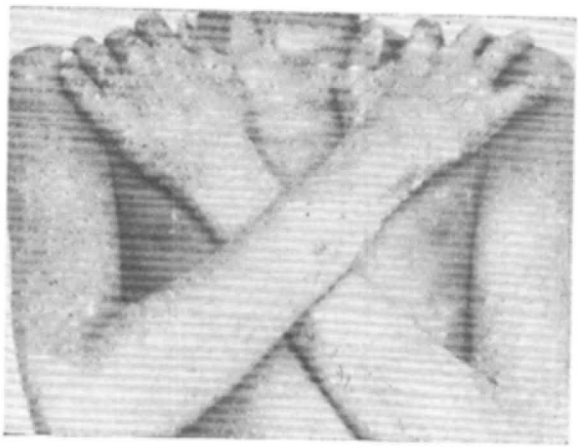

Fig. 1
Abnormal response to mosquito bites in cancer patients (lymphoma). Note discrete papules on uncoverd areas of body.

Fig. 2
A case of Carcinoma of cervix uterus. Note papular urticaria on exposed areas.

TABLE 3

Mosquito bite : Direct observation in various groups.

Sl. No.	Type of reaction	Mosquito bite : Direct Observation				
		Group I 30 cases	Group II 15 cases	Group III 15 cases	Group IV 25 cases	Group V 15 cases
1.	Immediate and delayed positive	26	Nil	Nil	Nil	Nil
2.	Immediate positive delayed negative	Nil	8	6	20	15
3	Immediate negative delayed positive	4	Nil	Nil	Nil	Nil
4.	No reaction	Nil	7	9	5	Nil
	Total	30	15	15	25	15

Histology

The papules induced by mosquito bites biopsied in 18 patients revealed moderate acanthosis in 14 specimens. No puncture canal by probocis could be seen in a few serial sections studied. Dermis showed moderate to dense collection of mononuclear cells around

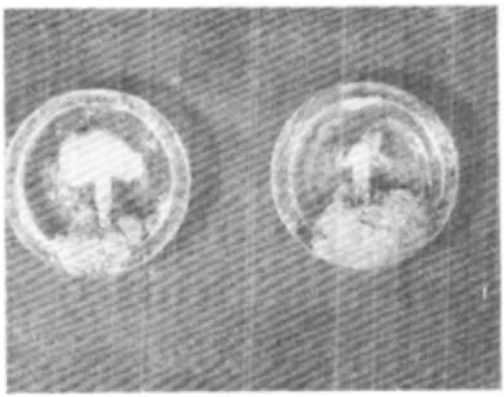

Fig. 3

LMT Test. Control and Test chambers. Note the fan like migration of white cells in control chamber. Note less migration in test chamber (Right). In lower part of the chamber is plasticine for attachment of capillary tube.

TABLE 4(a)

Leucocyte migration inhibition test in Cancer patients with abnormal response to mosquito bite.

Sl. No.	Type of Malignancy	Average absolute migration in sq. cm.		Migration Index MI	% of inhibition in test
		Test	Control		
1.	Ca. breast	0.111	0.432	0.256	75
2.	Ca. breast	0.123	0.512	0.240	76
3.	Ca. alveolus	0.209	0.382	0.547	46
4.	Ca. thyroid	0.135	0.444	0.304	70
5.	Ca. cervix	0.450	0.413	1.087	—
6.	Ca. oesophagus	0.104	0.518	0.200	80
7.	Ca. cervix	—	—	—	—
8.	Ca. breast	0.104	0.580	0.179	83
9.	Ca. breast	0.246	0.432	0.569	44
10.	Ca. cheek	0.209	0.648	0.322	68

TABLE 4(b)

Leucocyte migration inhibition test in healthy volunteers.

Sl. No.	Average absolute migration in sq. cm		Migration Index (MI)	% of inhibition of test
	Test	Control		
1.	0.401	0.432	0.928	8
2.	0.425	0.382	0.382	–
3.	0.493	0,401	0.401	–
4.	0.456	0.493	0.493	8
5.	0.345	0.401	0.401	14

blood vessels of the upper and mid dermis in all sections (Figs. 4 & 5). In 10 specimens the infiltrate was formed of eosinophils and mononuclear cells. Dermal oedema was seen in 12 specimens. The sites of positive delayed response to MSA were studied histologically in 5 cases. There was no significant epidermal changes. Perivascular mononuclear cell infiltration was noted in all the 5 specimens and 3 had an admixture of eosinophils also. The pathological changes were limited to the upper dermis.

Discussion

Nature has its own device of subduing the ill effects produced in man by insects, including mosquitoes. Though intensely pruritic indurated papules develop during early childhood, by the age of about seven years most individuals get desensitised to the antigenic material present in the saliva of mosquitoes. So the usual events following

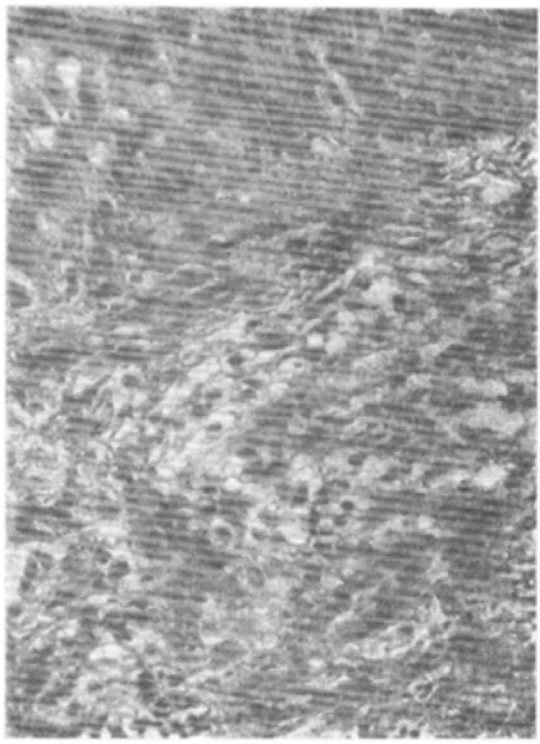

Fig. 4

Histolog of early papule after mosqito bite in a cancer patient. Infiltration around vessels with mononuclear cells and a few eosinophils.

mosquito bites after middle age is either no reaction or a mild transient wheal which does not cause much discomfort. But an unusual cutaneous eruption closely simulating 'papular urticaria' of childhood was observed in adult cancer patients. How the cutaneous events of early childhood reappeared in these adult patients with cancer in response to mosquito bites was a perplexing unanswered question to us. A detailed clinical, immunological and histological study was carried out to throw, light on the aetiopathogenesis of this abnormal response.

The number of patients who showed this abnormal response was low (30 among 500). The commonest age group in the present series was 41-50, which is quite different from the age group affected by papular urticaria which is usually 4 to 7 years[8,9]. The abnormal cutaneous response observed in 3 of our patients with atopic background cannot to attributed to atopy because recent reports [17,18] reveal that though atopics are liable to develop severe immediate reaction, the chances of their developing delayed (CMI) reaction is not more than normal and may be even less than normal.

Clinically the skin lesions had typical features of papular urticaria. Limitation of the lesions to uncovered area was characteristic especially on the unclad area on waist and upper arms. The central haemorrhagic puncta, the 'convincing proof' of mosquito bites[19] were noted in most of the lesions (Fig 6). Though the male to female ratio of 500 cancer patients admitted in the ward was 1 : 1.2, it was found that 27 of the 30 patients with abnormal response to mosquito bites were females. Such a predilection to the female sex can be attributed to the fact that, in the present study, the carcinoma affecting two organs-breasts

and the cervix uteri–of this sex group were the commonest sufferers with abnormal response to mosquito bites. Among 500 cancer patients, 128 (26%) had carcinoma affecting their cheeks. But only one among them showed abnormal response to mosquito bites. The patients with carcinoma of the cervix or the breast were receiving irradiation on abdomino-pelvic region (to induce artificial menopause in the latter group). The radiation at these sites are known to cause maximum immunosuppressive effect[20]. Though females on the basis of their high oestrogen content in body are more prone to be attracted by the mosquitoes[21], the exaggerated delayed reaction to mosquito bites they developed, cannot be attributed to the high level of oestrogen, since such a response is not seen in all women.

The MSA intradermal test and the direct observation of the sites of bites by mosquitoes in various groups revealed the following facts.

(a) The patients with clinical features of exaggerated reaction to mosquito bites showed an increased incidence of delayed reaction to ID test. (b) None of the 15 healthy volunteers showed abnormal cutaneous response to mosquito bites or to ID test with MSA. (c) Patients with diseases other than cancer behaved similar to healthy volunteers in their responsce to ID test and mosquito bites. (d) The therapy for cancer positively influenced the pattern of reaction to ID test as well as to the mosquito bites. Patients after irradiation and/or chemotherapy showed a higher incidence of immediate reaction than before therapy and developed delayed reaction to mosquito bites and to ID test with MSA which were not noted before therapy.

Fig. 5

Histology of delayed papule. Note dense collection of mononuclear cells around the blood vessels.

Fig. 6

Close view. Note central haemorrhagic puncta "The convincing proof" of mosquito bites.

Though mosquito antigen has been used as a mitogenic (blastogenic) agent in lymphoblast transformation test by Goh[22], there are no reports of its use in LMI test. The LMI tests have found wide use in immunopathology as an indicator of delayed immunity in man. The application of these tests in investigative dermatology, however, has been limited by the difficulties often met with in preparing proper antigen. The result of LMI test in the present study revealed that (a) the antigen (MSA) prepared was specific, inhibiting the migration of leucocytes of patients with abnormal response to mosquito bites, thereby acting as a delayed antigen. (b) It proved the lack of delayed hypersensitivity to MSA in 5 healthy volunteers.

The histologic features at sites of mosquito bites depend on the degree and type of allergic sensitivity rather than on species. In the present series perivascular mononuclear cell infiltration was evident in all the cases. Eosinophils also were seen in 10 specimens. This correlates with the clinical observation of biphasic lesions in our cases. Disruption of collagen seen in two of our specimens is similar to that observed by Weed[3]. The epidermal changes of hyperkeratosis and acanthosis can be attributed to the chronic and pruritic nature of the skin lesions. Puncture canals due to passage of probocis of mosquito, as noted by Goldman et al[23] could not be demonstrated in a few specimens where serial sections were made. The site of delayed positive reaction to ID test with MSA revealed similar perivascular mononuclear and eosinophilic cellular infiltration, but limited to the upper dermis alone. Though the ID test antigen is introduced only just below the epidermis, the probocis of mosquito reach much deeper into the dermis[13]. This may explain the lack of inflammatory infiltrate in the mid and deep dermis in the test induced papules.

To exclude the possibility that the cause for this abnormal cutaneous response is the lack of natural desensitisation (tolerance) to the bites of culex mosquitoes previously was excluded by close observation of a few attendants of the patients who were living with the patients for the previous five years in the same environment. None of the attendants developed exaggerated reaction to mosquito bites while in the ward, showing that they were naturally desensitised to the salivary antigen of the culex mosquitoes. The sudden development of exaggerated delayed reaction to their bites in only cancer patients implies loss of their acquired natural desensitisation of hypersensitivity to the salivary antigen of culex mosquitoes.

The immunological basis of hyposensitisation is still unresolved. More

recently it has been suggested that a separate class of thymic derived cells– Suppressor T Cells – act as negative regulators inhibiting the two basic types of immunological processes – the cell mediated and the humoral antibody mediated[24]. These Suppressor T cells play an active role in maintaining immunological tolerance. Loss of Suppressor T cell activity has been implicated, recently in the pathogenesis of auto immue disorders and Ig E dependent allergic diseases[24]. We put forward a new postulation to explain the exaggerated delayed response to bites of mosquitoes in these cancer patients. In the natural process of desensitisation to the mosquito venom due to repeated bites (tolerance) as occurs by the age of about 7 years, the lymphocytes which are sensitised to the salivary antigen (T. lymphocytes) get suppressed by Suppressor T cells. Loss of this Suppressor T cell activity through any cause can lead to the abolition of acquired tolerance. It is well known that therapeutic irradiation and cytotoxic drugs have got direct lymphocytotoxic effect. Significant lymphopenia occurs after whole body irradiation to a dose as little as 25 rads. The lymphocytes and germ cells are uniquely sensitive to radiation[25]. Though not reported so far to the best of our knowledge, it is possible that these Suppressor T cells can also be destroyed by irradiation which in turn lead to proliferation and activity of T lymphocytes specifically sensitised to mosquito salivary antigen and are mobilised to the site of injection of venom causing exaggerated delayed reaction clinically.

Recently, Suppressor T cells have been claimed to have significant role in determining the prognosis of cancer. The tumour cells contain antigen on their surface which are foreign to the host. In patients having increased Suppresssor T cell activity anergy is seen clinically and no CMI functions. Loss or decreased Suppressor T cell activity leads to mobilisation of T cells and help in immune elimination of tumour cells[24]. So even without irradiation decrease in activity of Suppressor T cells and thereby increase in CMI can occur. This will explain why one of our patients developed abnormal response to mosquito bites even when he was not receiving any chemo or radiotherapy.

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