

DEPRESSION OF DELAYED TYPE HYPERSENSITIVITY TO OLD TUBERCULIN IN PATIENTS WITH CERVICAL CANCER

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Delayed type hypersensitivity to Old Tuberculin in patients with cervical cancer has been studied. A depression in both incidence and intensity of hypersensitivity of this type is found in them. The depression seems related closely to the clinical staging and presence of lymphatic metastases. It becomes more evident in those suffering from recurrent lesion or under irradiation therapy. The underlying mechanism is still obscure though many authors have suggested that it may be due to an immunological defect. Whatever it may be, once the immunological response is impaired, it seems to persist even after successful surgical removal of the primary tumor. Therefore, a certain immunotherapy might have some place in the treatment of the malignant disease.

The essential nature of delayed type hypersensitivity is generally believed to be a reaction between antigen and sensitized lymphocytes which, in turn, play an important role in the cellular component of immunological defense mechanism. There are a wide variety of antigens, including bacterial, fungal, protozoal, viral or even chemical substances, which are capable of producing reaction of this type. Tuberculin protein is one of the most classical antigens. It has been known for a long time that a suppression in Tuberculin reaction may occur in cancer patients. The suppression is commonly regarded as being related to the accompanying debility, rather than to malignant tumor itself. However, some authors^(1,4,7,8) have offered an attractive proposition that a specific immunological depression may be responsible for the suppression of the hypersensitivity. The purpose of the present program is to study the delayed type hypersensitivity to Tuberculin in patients with cervical cancer of the uterus. A brief review of the literature is also presented.

MATERIALS

Controls: 14 healthy young nurses who had had B. C. G. vaccination in childhood and 74 women with benign lesions (e. g., cervical erosion, myoma, prolapse of the uterus, adenomyosis, sterility, ovarian cyst, condyloma, etc.) were subjected to a Mantoux test. None of the 74 women have a history or roentgenological evidence of active pulmonary tuberculosis and all of them had a cervical biopsy and were found to be free from cancer of the cervix. Of these, only two had had B. C. G. vaccination in childhood.

Cancer patients: Mantoux test was carried out before therapy in 46 (38 primary disease and 8 recurrences), during the course of irradiation therapy and/or chemotherapy in 15, and after therapy (all but 3 had radical surgery) in 102 women. The general condition of these women was little affected with the exception of a Stage IV patient with lung metastasis and 4 patients with recurrence. Active pulmonary tuberculosis was found in a Stage 0 patient tested before surgery.

METHOD

Old Tuberculin of 10 T. U. was used as the antigen. It was considered preferable to P. P. D. in the present study since our primary concern is the delayed type hypersensitivity itself, and not the specificity for past tuberculous infection. 0.1 cc of O. T. was injected intradermally into a forearm. Reading was taken from 48 to 72 hours later. Erythema and/or infiltration larger than 10 mm in diameter was taken as a positive response.

RESULTS

Tuberculin reaction in controls: Of 14 healthy nurses who had had B. C. G. vaccination, 12 or 85.7% showed positive reaction.

Of 74 women with benign lesions, 55 or 74.3% showed positive reaction.

Tuberculin reaction in cancer patients: A depression of Tuberculin reaction was demonstrated in cancer patients whether they were submitted to the test before, during or after the treatment. The depression was mild in 38 primary cases, of whom 23 or 60.5% gave positive response ($\chi^2 = 2.26$, $p = 0.137$). A highly significant depression was found in the post-treatment group where 55 or 53.9% of 102 women showed positive response ($\chi^2 = 7.6$, $p = 0.006$). In 8 recurrent cases and 15 cases receiving irradiation and/or chemotherapy, a marked depression to 25% and 20% was noted respectively.

Table I. Suppression of Tuberculin reaction in cancer patients

Category of patients	Number of cases	Positive reaction %
Healthy nurses	14	85.7
Women with benign lesions	74	74.3
Cancer patients		
before therapy	38	60.5
after therapy	102	53.9
under therapy	15	20.0
recurrent	8	25.0

Reactivity to different strength of antigen:

To a limited number of subjects who showed negative reaction to Tuberculin of 10 T. U., a second test utilizing Tuberculin of 100 T. U. as antigen was carried out to see their responses. Of 6 controls with negative reaction, 4 or 66.7% responded with 100 T. U. whereas only 10 or 45.4% of 22 cancer patients with negative reaction responded with 100 T. U.

DISCUSSION

It has been known for a long time that there is a suppression in delayed type hypersensitivity in cancer patients since the first description by Jousset⁽¹¹⁾ in 1926. However, after a thorough review of the literature, we

found that there is no general agreement as yet (Table II). Some^(1,11,16,18) claim that the depression occurs only in advanced or terminal patients and some⁽⁷⁾ insist it is present even in early cases. Fairley and Matthias⁽⁸⁾ have reported 27.5% of reticulosis, 42% of carcinoma and 71% of controls responded to 10 T. U., whereas 25% of reticulosis, 40% of carcinoma and 17% of controls failed to respond to 10 T. U. but still could respond to 100 T. U. The results of the present study reveal that the delayed type hypersensitivity in cancer patients is depressed in both incidence and intensity.

Apparently, there are many factors which might influence the delayed type hypersen-

Table II. Review of the literature

Authors	Category of patients	Number of cases	Positive reaction (%)
Renaud (1926)	Early cancer	32	68.8
	Advanced cancer	18	0
Fairley, Matthias (1960)	Control	116	88
	Carcinoma	43	82
	Reticulosis	138	55
Lamb, Pilney, Kelly and Good (1962)	Control	208	52
	Carcinoma in good condition		34
	Carcinoma in poor condition		9
Graham, Graham (1964)	Control		30-40
	Cervical cancer St. I		25
	Cervical cancer St. II		18
	Cervical cancer St. III, IV		14
Hughes, MacKay (1965)	Control	122	81
	Cancer	122	52
Ashikawa et al (1967)	Control	356	69.1
	Cancer (terminal)	325	32.5
Israel et al (1967)	Control (Coury's)		78-91
	Cancer before therapy	80	57.5
	Cancer after therapy	50	40
Rieche, Bacigalupo (1968)	Breast cancer early	65	74
	Breast cancer late	55	40

sensitivity to Tuberculin. Hinshaw⁽⁶⁾, in his monograph on diseases of the chest, has listed several conditions in which anergy may occur. These conditions are; (1) overwhelming tuberculosis, (2) acute febrile and exanthematous diseases, (3) sarcoidosis, leukemia or lymphoma, (4) prolonged treatment with anti-inflammatory drugs of cortisone type and (5) conditions of marked debility, including malnutrition and senility. Factors such as age, general condition, surgical stress, extension of the lesion and histological types will be discussed here.

Age: Johnston *et al*⁽¹⁰⁾ have pointed out that there is a progressive decline in Tuberculin sensitivity in old aged people in terms of incidence and intensity of the reaction, probably due to nonspecific senile loss in skin reactivity⁽¹⁵⁾. In the present series, no definite

correlation was confirmed between the age and the response in both control and cancer groups (Tables III and IV).

Table III. Factor which might influence Tuberculin reaction: 1. Age of cancer patients prior to therapy

Age	Number of patients	Positive reaction	
		No.	%
31-40	9	4	44.5
41-50	17 (21)	11 (13)	64.7 (61.9)
51-60	6 (10)	3	50.0 (30.0)
61-70	5	4	80.0
71-	1	1	100.0
Mean: 47.3	38 (46)	23 (25)	60.5 (54.3)

N. B. Figures in parenthesis indicate number including recurrent cases

Table IV. Factor which might influence Tuberculin reaction: 1. Age of cancer patients after therapy

Age	No. of cases	Positive reaction	
		No.	%
-30	2	1	50.0
31-40	21	17	80.9
41-50	49	27	55.1
51-60	21	6	28.6
61-70	9	4	44.4
Mean: 47.6	102	55	53.9

General condition: The fact that a more evident depression occurs in advanced cancer cases, naturally leads one to the view that

the depression is attributed to the accompanying debility of the patients rather than to the tumor itself. Lamb *et al*⁽¹²⁾ have described that a patient was anergic only very infrequently when in good condition, but was anergic in relatively high frequency when in poor condition (Table II). On the contrary. Levin *et al*⁽¹³⁾ have recorded normal response in patients of debilitating, non-cancerous diseases. Lytton *et al*⁽¹⁴⁾ have reported that response of patients with malignant disease to tetanus toxoid was impaired but was not related to the general physical condition or to advancing ages. Most patients of the present series are in good health; 4 of 8 patients suffering from recurrence were in poor condition (Table V).

Table V. Factor which might influence Tuberculin reaction: 2. General condition

Case	Age	Site of recurrence	General condition	Tuberculin reaction
1. Renn HY	55	Pelvis	good	-
2. Chen LHM	44	Urethra	good	+
3. Cheng CI	48	Rectum	good	-
4. Chen C	48	Pelvis	good	-
5. Wu MH	44	Abd. wall	poor	++
6. Wang TC	54	Lung	poor	-
7. Lin HPY	52	Lung	poor	-
8. Chen Ly	53	Intestine	poor	-

No difference in incidence of anergy was noted between those in good condition and those in poor condition. The 5th case, Wu MH who was in cachectic state with uremia, gave a positive reaction until one week before her death.

Surgical stress: In order to see whether great stress of extensive radical operation might have a temporary suppressive effect on the patient, in 19 patients Mantoux test was carried out before and after operation. The skin response was unchanged in about half of them, suppressed in 26.3% (one turned into negative), and intensified in the

remaining 21.1% (Table VI). In the postoperative group, correlation between reactivity and postoperative years was studied but no positive correlation was found (Table VII). This result is consistent with that of Hughes and MacKay⁽⁷⁾ who have found that the reaction is essentially the same for those tested preoperatively and postoperatively in both controls and cancer patients; in 10 patients who had tests before and after operation, they have observed only a minor difference in the over-all incidence of anergy, but they did not mention the change in reactivity in individual cases. They have described

Table VI. Factor which might influence Tuberculin reaction: 3. Surgical stress

Change in response	Histological diagnosis	Stage	Lymphnode
Intensified 21.1%	Epidermoid	0	—
	Epidermoid	I	0/23
	Epidermoid	I	0/39
	Adenocarcinoma	IIb	3/27
Suppressed 26.3%	Epidermoid	I	0/31
	Epidermoid	I	11/29
	Epidermoid	IIa	0/36
	Epidermoid	IIb	0/33
Remain unchanged 52.6%	Epidermoid	IIb	0/34
	Epidermoid	I	0/40
	Epidermoid	I	0/50
	Epidermoid	IIa	0/36
	Epidermoid	IIb	3/33
	Epidermoid	IIb	1/42
	Epidermoid	IIb	1/37
	Adenocarcinoma	III	0/37
	Adenocarcinoma	IV	2/33
	Epidermoid	IV	1/48
Epidermoid	IV	—	

Table VII. Factor which might influence Tuberculin reaction: 3. Surgical stress

Time interval (year)	Number of cases	Positive reaction	
		No.	%
-1	47	24	51.1
1-2	22	10	45.5
2-3	12	9	75.0
3-4	8	4	50.0
4-5	8	6	75.0
5	5	2	40.0

two cases in whom Tuberculin response has become strongly positive after surgery. We hesitate to agree with their hasty conclusion that the depression in immune mechanism may be reversed by successful curative surgery.

Extent of the lesion: Most authors believe the depression in delayed type hypersensitivity occurs only in advanced cancer patients (Table II). Nevertheless, Hughes and Mack-

ay⁽⁷⁾ claim that such depression can be observed as well in early breast cancer; in their series, 63% gave positive response in contrast to 96% of controls. This is rather open to discussion, since what they meant by "early cases" actually consisted not only of cases with localized tumor, but also of cases with regional lymphnode involvement. In the present series, as shown in Table VIII, the depression in hypersensitivity becomes more

evident as the clinical stage advances; 66.6% of cases of Stages 0 and I show positive reaction while 56.5% of cases of Stages II, III and IV show positive reaction. Graham and Graham⁽⁴⁾ have also found that the frequency of positive Tuberculin test, in cancer of the cervix, is lower and is inversely proportional to the clinical staging of disease (Table II). Correlation between reactivity

and lymphatic metastasis has been studied in the present series; of 38 cases tested before therapy, 23 had radical operation with pelvic lymphadenectomy, thereafter 9 of them had lymphatic involvement, of whom only 44.4% gave positive reaction in marked contrast to 71.4% of those without lymphatic metastasis (Table IX).

Table VIII. Factor which might influence Tuberculin reaction:

4. Extension of the lesion

Clinical staging	No. of cases	Positive reaction	
		No.	%
0	3	1	33.3
I	12	9	75.0
IIa	8	6	75.0
IIb	7	3	42.8
II	4	1	25.0
IV	4	3	75.0
controls	74	55	74.3

Table IX. Factor which might influence Tuberculin reaction: 4. Extension of the lesion; lymphatic metastasis

	Number of cases	Positive reaction	
		No.	%
Before therapy			
metastasis (+)	9	4	44.4
metastasis (-)	14	10	71.4
After therapy			
metastasis (+)	19	8	42.1
metastasis (-)	83	47	56.6
Controls	74	55	74.3

Histological type of the tumor: Tuberculin reaction seemed to be more suppressed in case of epidermoid type (Table X). No conclusion can be reached before more data are collected. Israël *et al.*⁽⁹⁾ have reported a more pronounced suppression of hypersensitivity in patients with small cell carcinoma. **Irradiation and chemotherapy:** It is well known that X-ray, radium or anticancer drugs

which interfere with cell division would prevent the development of delayed type hypersensitivity⁽⁸⁾. Of 12 patients receiving irradiation therapy with radium or Co⁶⁰, only 2 or 16.6% gave positive reaction. Neither of the 2 patients who had irradiation and chemotherapy showed positive response (Table XI). In animal experiments, it is well proven that the depression of delayed type

Table X. Factor which might influence Tuberculin reaction: 5. Histological types

Histological types	No. of cases	Positive reaction	
		No.	%
Before therapy			
Epidermoid ca.	33	19	57.9
Adenocarcinoma	3	3	100.0
Adenoepithelioma	2	1	50
After therapy			
Epidermoid ca.	97	52	53.6
Adenocarcinoma	4	3	75.0
Mixed tumor	1	0	0

Table XI. Factor which might influence Tuberculin reaction: 6. Effect of irradiation and chemotherapy

Category of patients	No. of cases	Positive reaction	
		No.	%
Before therapy	46	22	54.3
Irradiation	12	2	16.6
Chemotherapy	1	1	100.0
Both	2	0	0

hypersensitivity can be produced by chemotherapeutic drugs by inhibiting the differentiation of small lymphocytes into immunoblasts, by interfering with the contact of antigens with mastcells or by inhibiting the DNA synthesis⁽²¹⁾. However, in clinical study, Rieche and Bacigalupo⁽¹⁸⁾ have refuted this, claiming that 11 of 15 patients who under or after chemotherapy showed positive reaction. Israel *et al*⁽⁹⁾ also emphasized that chemotherapy had little effect on the delayed type hypersensitivity; after chemotherapy of 2-21 months' duration, 15 remained positive and 8 remained negative. Blomgren *et al*⁽²⁾ and Hersch *et al*⁽⁵⁾ have demonstrated that humoral immune mechanism is more affected by chemotherapy than cellular.

Mechanism of depression in delayed type hypersensitivity: It has been a subject of discussion for many years as to why such depression is present. Rieche & Bacigalupo⁽¹⁸⁾

have reported a suppression to 40% in late stage breast cancer and considered that this might be related to the elevated level of serum corticosteroids usually found in these patients. Hughes & MacKay⁽⁷⁾ have suggested that the early depression is due to a specific immunological depression. They thought this might be caused by the uptake by the tumor of some essential metabolite of lymphoid cells, or the tumor might produce a substance which depressed the lympho-reticular system. Another interesting explanation suggested by them is an antigen competition hypothesis. The patient may be responding so well to a cancer specific antigen in the tumor that he is unable to respond adequately to further exogenous stimulation. Graham and Graham⁽⁴⁾ have suggested that a "tolerance agent" might be present in cancer patients, by demonstrating patients' tolerance to homotransplanted tumor or normal tissue;

cancerous tissue implanted in normal volunteer is promptly rejected within 7-10 days, rarely survives more than 2 weeks, but in 44 to 150 of patients with primary cancer of the cervix, skin homotransplants are tolerated for more than 2 weeks. Sekiguch *et al*⁽¹⁰⁾ have demonstrated, in animal experiments, some defect in the immunological competence of lymphoid cells from tumor bearing animals—the transplantation of bone marrow cells from tumor bearing parents into F₁ hybrid mice induced higher grade of secondary disease than that when the grafted cells were derived from healthy parents. With human lymphocytes, Ricci *et al*⁽¹⁷⁾ proved that the lymphocytes from cancer patients were less responsive in vitro to foreign antigen as compared with those from normal individuals. Ashikawa *et al*⁽¹⁾ have demonstrated a marked suppression of Tuberculin test in cancer patients and that B. C. G. vaccination hardly elicited a positive reaction in those patients. On the other hand, the humoral antibody to phosphatide fraction of Tubercle bacilli was detected in subnormal level and was capable of increasing to a nearly normal level with B. C. G. vaccination. They concluded that there is a dissociation between two types of immunological reactions—humoral response and cell mediated one, and that the dissociation becomes more marked in the later course of cancer.

Prognosis: Israël *et al*⁽⁹⁾ have found that cancer patients with negative Tuberculin test had a worse prognosis than those who had positive reaction; of 19 patients with negative reaction, 79% died within 6 months, in contrast to 19% of 31 positive cases. This is consistent with the result of Hugher & MacKay⁽⁷⁾ who have found 9 or 81.8% of dead patients gave anergy while only 3 or 33.3% of 9 survivors gave negative response. In our clinic, it is a routine procedure to carry out a Mantoux test on every patient with cervical cancer before treatment, hence,

the correlation between the delayed type hypersensitivity and the prognosis of the patient will be clarified in 5 years.

CONCLUSIONS

A study of delayed type hypersensitivity to Old Tuberculin in controls and cervical patients has obtained results as follows:

1. A mild depression of Tuberculin was noted in cancer patients before therapy, of whom 60.5% gave a positive reaction in contrast to 74.3% of controls. The depression was more eminent in patients after therapy (53.9%) or under therapy (20.0%) or those with recurrent lesion (25%).
2. The depression in reactivity was also noted; only 45.4% of them responded with 100 T. U. in contrast to 66.7% of controls.
3. The depression seemed to be related closely to the clinical staging and presence of lymphatic metastasis. 66.6% of early cases (Stages O & I) and 56.5% of advanced cases (Stages II, III & IV) showed positive response. 71.4% of cases without lymphatic metastasis gave positive response whereas only 44.4% of those with lymphatic metastasis did so.
4. The underlying mechanism of the suppression is obscure, however, once the impairment is established, it seems to persist even after a successful surgery. Correction of such impairment by a certain immunotherapy might contribute to a better prognosis.

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子宮頸癌病人對 Old Tuberculin 之遲發性過敏反應

臺北醫學院婦產科

鄭永盛 徐千田

我們以尚未開始治療之癌病人 38 名，治療後健康者 102 名，正在照射或化學藥物治療中的病人 15 名以及再發病人 8 名為對象，作 Tuberculin 反應，同時以患良性疾病(如肌瘤，子宮頸糜爛，卵巢囊腫等)之婦人 74 名為對照羣，比較檢討之結果，獲得如下結論：

- 1) Tuberculin 反應陽性率：對照羣為 74.3%，尚未開始治療之癌病人為 60.5%，治療後目前健康婦人為 53.9%，接受照射或化學藥物治療者為 20%，再發病人為 25%。
- 2) 子宮頸癌病人不但陽性率低，同時反應力亦較弱

，對 100 T. U. 抗原對照羣 66.7% 有反應，但癌病人只有 45.4% 有反應。

- 3) 早期癌(0 期及 I 期)之陽性率為 66.6%，晚期癌(II, III, 及 IV 期)為 56.5%。淋巴腺有轉移者只有 44.4% 之陽性率，但無轉移者却高達 71.4%。
- 4) 這種遲發性過敏反應之抑制，其發生機轉，尚不明瞭，但如一旦受到抑制，雖經開刀，癌症治療後照舊繼續存在，因此如何來改善病人之抗體產生能力將是今後重要研究課題之一。