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Kveim Test in leprosy: a clinical and histopathological evaluation

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Summary The gross appearances and microscopic features of Kveim tests were studied in 21 North Indian leprosy patients. Of 6 patients with tuberculoid leprosy, 2 showed positive reactions and a close correlation between nodule formation and granulomatous histology. Of 15 patients with lepromatous leprosy, only 1 patient (who showed no evidence of a papule or induration at the Kveim test site) yielded a positive response microscopically. These findings suggest the occurrence of a low level of Kveim reactivity in North Indian leprosy patients. However, it is suggested that further studies with proper controls should be carried out to eliminate the possibilities of chance inclusion of subclinical leprotic skin lesion at the site of Kveim antigen injection and needle trauma in triggering or accelerating granulomatous inflammation.

Introduction

The specificity of Kveim test in sarcoidosis has been debated and challenged for years.[1–9] More recently, a number of publications have strongly supported its specificity in sarcoidosis.[10–13] However, using validated Kveim preparations, it has been concluded that positive Kveim reactions do occur in all varieties of leprosy but are infrequent, except in Chinese and Japanese patients who show a higher frequency of positive tests.[14–18] This study was undertaken to test validated Kveim antigen CR-I[11] in North Indian leprosy patients.

Material and methods

Twenty-one patients of different types of leprosy[19] attending the leprosy clinic of the Nehru Hospital attached to the Postgraduate Institute of Medical

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Education and Research, Chandigarh, India, were tested with validated Kveim antigen CR-I. 0.15 ml of the test material was injected on the forearm. The exact site was identified by measuring the predetermined distance from the India ink spot tattoed in the forearm skin. All of the patients had been tested with 1 unit of PPD (Serum Institute, Copenhagen), and only negative reactors were included in the study. The patients were thoroughly screened for evidence of active tuberculosis, sarcoidosis, or any other chronic disease.

Lepromin test was carried out with 0.15 ml of standard lepromin (having 160–200 million bacilli/ml) on all the patients and was read after 4 weeks, and if negative, after 6 weeks. The test was considered negative if there was less than 4 mm induration.

Age, sex, duration of the disease, and treatment were not taken into consideration. None of the patients had received any steroid, immunosuppressive or other anti-inflammatory drugs within the past 3 months.

Biopsy specimens from Kveim antigen sites, irrespective of the induration, were taken after 40 ± 2 days and were stained with haematoxylin and eosin stains, and Fite-Faraco stain for the demonstration of acid-fast bacilli. The biopsies were graded as positive, equivocal, or negative according to the criteria of Siltzbach and Ehrlich[20] and those of Mitchell.[21] Biopsy specimens were separately screened by 2 different pathologists who were not aware of the type of study.

Results

Out of the 21 patients studied, 4 were polar tuberculoid (TT), 2 were borderline (BT), 10 belonged to the borderline lepromatous (BL) group, and 5 were of the polar lepromatous (LL) type. For purposes of discussion, BT patients have been included in the TT group and BL in the LL group, as shown in Table 1. Duration of the disease was more than 3 years in all patients, and each patient had taken the treatment for over 2 years.

Lepromin reaction was positive (induration of 4.5 mm or more) in all the TT and BT patients, and negative in all BL and LL patients.

The Kveim test was positive in 3 patients, 2 in the TT group (Figure 1) and 1 in the LL group (Figure 2). In the TT group both patients showed a nodule formation and positive histology, whereas in the LL group the positive histology was seen in the absence of any detectable induration (Table 1). In addition, the biopsies in 1 patient in the TT group and 2 in the LL group showed moderate chronic inflammatory cellular response with no specific granuloma formation.

Table 1. The age, sex, type of leprosy, positive reactions, and histopathology

No.	Name/Age/Sex/Type of Leprosy/Duration of disease	Reaction to Kveim Antigen	Grouping of patients for study	Histo-pathological findings
1	L/40/M/BT/4 yrs	+	TT	—
2	RSS/35/M/TT/3 yrs	—	TT	±
3	D/25/M/TT/5 yrs	+	TT	+
4	RN/35/M/BT/3 yrs	—	TT	—
5	SK/35/F/TT/5 yrs	—	TT	+
6	AK/45/F/55/4 yrs	+	TT	—
7	AR/45/M/BL/8 yrs	—	LL	—
8	SL/40/M/BL/3 yrs	+	LL	—
9	MPN/50/M/BL/6 yrs	—	LL	—
10	RD/45/M/BL/4 yrs	—	LL	—
11	JS/55/M/BL/3 yrs	—	LL	—
12	S/20/F/BL/4 yrs	—	LL	—
13	SS/50/M/BL/4 yrs	—	LL	—
14	K/35/F/BL/5 yrs	—	LL	±
15	BS/60/M/BL/10 yrs	—	LL	±
16	L/20/F/BL/4 yrs	—	LL	+
17	H/35/M/LL/5 yrs	—	LL	—
18	KD/45/F/LL/5 yrs	—	LL	—
19	LB/20/M/LL/5 yrs	—	LL	—
20	RR/30/M/LL/5 yrs	—	LL	—
21	BR/40/M/LL/10 yrs	—	LL	—

BT Borderline tuberculoid. LL Polar lepromatous.
BL Borderline lepromatous. TT Polar Tuberculoid.
— Negative + Induration up to 5 mm.

Histopathological changes:
— None to mild. Nonspecific inflammation.
± Equivocal. Moderate inflammation with no classical granuloma formation.
+ Positive. Classical epithelioid granuloma with or without giant cells.

Discussion

Since the first use of test material reported by Williams and Nickerson,[22] subsequently named Kveim antigen,[23] conflicting reports appeared in the literature regarding the specificity of Kveim test. While some authors accepted false positive Kveim test rate in the range of < or = 3%[6,24,25] others claimed much higher positive rates in a variety of diseases other than sarcoidosis.[4,14,15,24,26–29] The lack of specificity of Kveim test was, in most part, attributed to unvalidated Kveim preparations.[30] Further, careful testing of Kveim antigens prepared from different sarcoidosis tissues have shown that less than half of these Kveim preparations may turn out to be specific enough as to warrant its use as a diagnostic reagent.[17] Although a number of recent publications strongly support the specificity of Kveim test,[10–13] the response

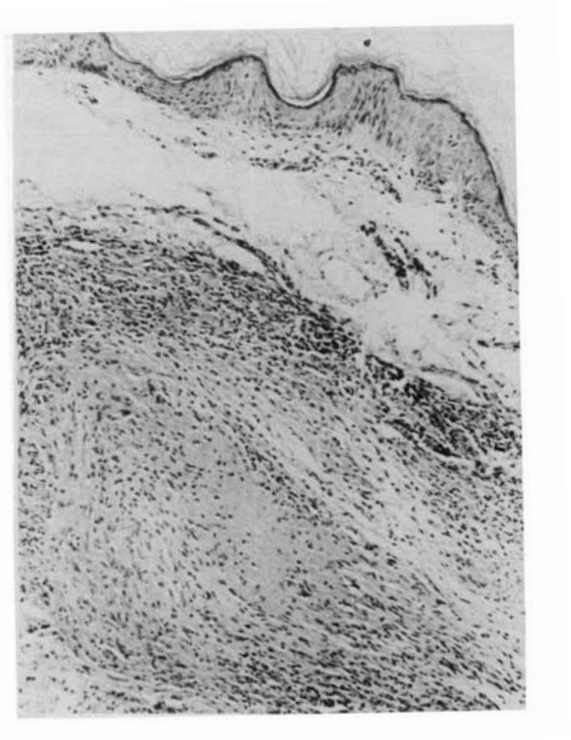

Figure 1. Typical granuloma in a tuberculoid case.

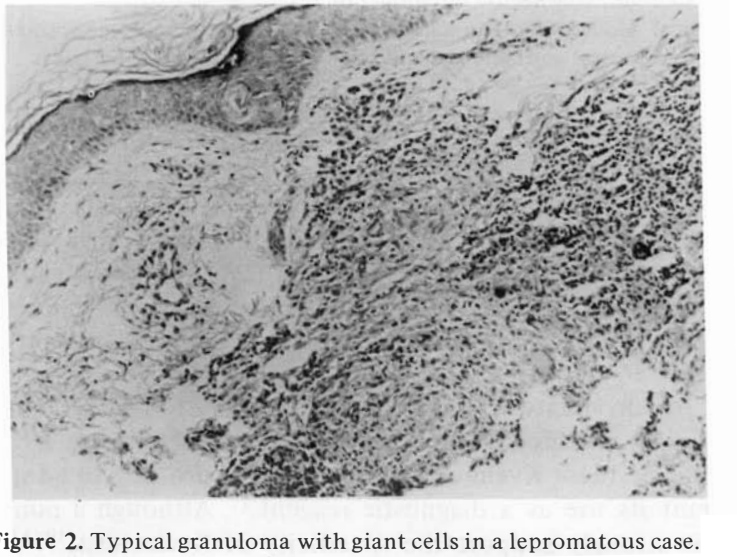

Figure 2. Typical granuloma with giant cells in a lepromatous case.

of leprosy patients to intradermal injection of Kveim antigen is a special matter because in an international study[6,7] in which a validated Kveim material was used, it showed a high frequency of positive Kveim test reactions among Japanese. Similar results were reported by Pearson *et al.*[14] and Rees[15] in Japanese and Malay patients with lepromatous leprosy, and by Hurley *et al.*[31] in lepromatous leprosy and ENL. In contrast, Pearson *et al.*,[14] Rees[15] and Hopper and Stuettgen,[32] using validated Kveim material, found no positive reactions among European, and Mendes *et al.*[27] in the Brazilian leprosy patients.

In the present study, 2 of the 6 tuberculoid patients (33%) gave positive histopathological response and 1 gave an equivocal result, whereas in the lepromatous group only 1 patient out of 15 (6.6%) gave positive reaction and the result was equivocal in 2. In the only study available from India, Krishnamurthy *et al.*[18] found positive rates of 36% among tuberculoid patients and 25% among lepromatous patients. Thus, our results show lower frequency of positive Kveim tests than those in Japanese[6,14,15] and South Indians.[18]

There is no clear explanation for the positive Kveim test reported in leprosy patients. It will be interesting to note that Bedi *et al.*[33] examined skin biopsies from clinically normal looking skin of the scalp, axillae and groins in 20 treated lepromatous leprosy patients and found that up to 25% of the patients had well-formed foam cell granulomas. Further, Klokke *et al.*[34] performed skin tests similar to Kveim tests on 7 patients with tuberculoid leprosy with a suspension of non-sarcoid human spleen and found that 3 of these patients had histologic evidence of granulomatous inflammation at the test site.

It appears that positive Kveim tests in leprosy patients could very well be due to the presence of occult granulomas present in the normal looking skin of these patients. The needle trauma could also be triggering or accelerating the granulomatous inflammation. It is suggested that further studies be carried out with inactivated Kveim antigen and normal saline as controls to finally settle the controversy of positive Kveim tests in leprosy.

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