THE ROLE OF PENTAVALENT Tc-99m DMSA IN THE DIFFERENTIAL DIAGNOSIS FOR CERVICAL LYMPHADENOPATHIES

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SUMMARY

Twenty patients with palpable cervical lymphadenopathy underwent Tc-99m (V) DMSA scintigraphy during their diagnostic work-up. In this prospective study, the scintigraphic findings were correlated with the clinical diagnoses and the results of the routine laboratory tests (complete blood count, biochemical analyses, chest X-ray, and tuberculin skin tests) and histopathological examinations of the excisional biopsy specimens.

In patients with tuberculous lymphadenitis (diagnosed clinically and histopathologically) the intense Tc-99m (V) DMSA uptake in the involved cervical lymph nodes was found to be significant.

In seems that Tc-99m (V) DMSA scintigraphy is a safe and non-invasive diagnostic imaging modality, that may be utilized in the initial work-up to assist in the differential diagnosis of cervical lymphadenopathies. The observed affinity of the radiopharmaceutical for mycobacteria-infected cervical lymph nodes seems to be congruent with the localization mechanism (i.e. structural similarity to phosphate ion) proposed by Ohta and his coworkers.

Key Words: Cervical lymphadenopathy, tuberculous lymphadenitis, mycobacterial lymphadenitis, Tc-99m (V) DMSA scintigraphy

INTRODUCTION

The enlargement of lymph nodes is called lymphadenopathy or adenomegaly. Lymph nodes play an important role in the defence system of the body via generation of immune response leading to elimination of foreign antigen. Afferent lymph, containing lymphocytes, macrophages and antigens enters the lymph node by the subcapsular space, and is drained into medullary sinuses that form efferent lymhatic vessels. The lymph leaves the nodes via efferent lymphatics.

The cervical lymph nodes are divided into two sets, superficial and deep. The superficial cervical nodes may be arranged in three sets consisting of submaxillary, subrahyoid and cervical. The deep cervical nodes are larger in size and more in number as compared to superficial nodes They form a chain along the sheath of the carotid artery and internal jugular vein and are further divided into two sets: an upper and a lower set that are situated along the upper and the lower part of the internal jugular vein, respectively.

Various complexes of technetium (Tc-99m) have been used to image lymph nodes (lymphoscintigraphy) and to image the cervical region organs such as the salivary glands, thyroid and parathyroid glands via qualitative ad quantitative methods in the diagnostic work-up of related pathology.

Yokoyama et al. developed pentavalent technetium-99m-labeled dimercaptosuccinic acid (Tc-99m (V) DMSA) that has two important characteristics: the affinity for tumour tissue and the optimal energy of gamma rays emmitted by Tc-99m that makes it detectable by gama camera (1). Ohta et al. reported uptake of Tc-99m (V) DMSA in medullary thyroid cancer and some soft tissue tumors (2,3).

The aim of this study is to evaluate the value of Tc-99m (V) DMSA scintigraphy as a diagnostic

procedure in the initial work-up of patients with cervical lymphadenopathy.

METHODS

The patient population includes 20 patients who presented with cervical lymphadenopathy to the outpatient clinics of the internal medicine and ear nose throat (ENT) departments of the Gulhane MilitaryMedical Academy. Eighteen patients were men, two were women and their ages ranged from 18 to 59, the mean age being 28.6. All of these patients underwent Tc-99m (V) DMSA scintigraphy before the final diagnosis was established and the therapy was initialized.

Following routine history taking and physical examination, a work-up including chest X-ray, CBC, ESR, peripheral smear, PPD and ultrasonography was performed for the etiological differential diagnosis of the cervical lymphadenopathy. The study group included patients with cervical lymphadenopathy. The study group included patients with cervical lymphadenopathy measuring at least 1x1 cm evaluated prospectively by pentavalent DMSA scintigraphy. These patients were further classified as "reactive lymphadenopathy" (either nodes disappeared after antibiotic therapy or they persisted and were biopsy-proven) and patients with specific diagnoses (established on clinical and histopathological grounds). The former served as the control group of the study. In the cases who were initially evaluated as nonspecific adenitis but did not respond to semisynthetic penicillin, excisional biopsy was performed before the specific therapy was initialized. In all of the cases Tc-99m (V) DMSA scintigraphy was performed prior to the lymph node biopsy.

Tc-99m (V) DMSA was prepared from a commercial lyophilized DMSA kit for renal imaging (Amersham International, UK). The kit containing 1.00 mg DMSA and 0.42 mg $SnCl_2$ in the vial was dissolved in 0.0833 ml of molar (8.4%) sodium bicarbonate solution. The pH of the solution was checked by a paper indicator. After confirmation of an alkaline medium, labeling was performed by the addition of 2-3 ml of technetium-99m pertechnetate with the desired activity (not to exceed 3 patients at a time with a dose of 15 mCi per patient). Tc-99m was obtained as pertechnetate by elution of a commercial generator (Amersham International, UK).

The quality control of the radiopharmaceutical was performed in two steps. The pH of the lyophilized kit dissolved in molar sodium bicarbonate was checked. The pH values were in the range of 7.6-8.0. Then the radiochemical purity of the complex was analyzed by thin layer chromatography (Merck silica gel, developed with n-butanol/acetic acid/H_2O (3:2:3), and no free pertechnetate or other Tc-99m derivative was detected.

Anterior, right and left lateral scintigrams of the head and neck region were obtained in each patient 2 and 90 min. after i.v. administration of 10 mCi Tc-99m (V) DMSA. A conventional gamma camera (Siemens, Orbiter Digitrac 3700) with low energy all purpose (LEAP) parallel hole collimator was used. The analog images of 500.000 counts were recorded via a multiformat camera on single emulsion films.

The scintigrams were evaluated on the view box by comparison of lymph node uptake of radioactivity with that of the nasopharyngeal region and were interpreted as no uptake (-), minimal uptake (+), uptake equal to or greater than the nasopharyngeal uptake (+ +) (Table II).

RESULTS

The demographic data, clinical, ultrasonographic ad scintigraphic findings and the final diagnoses of the patients are summarized in Table II. On clinical examination, the localization, consistency and size of the cervical lymph nodes were assessed. The size of the largest cervical lymph node as measured via ultrasonography in each patient appears in Table II.

Out of the 7 cases showing intense uptake of pentavalent DMSA in the prospective scintigraphic study, the diagnoses of mycobacterial lymphadenitis, neoplasia, and chronic infection with abscess formation were established clinically and histopathologically in 4, 2 and 1 case (s), respectively (Table I).

In patients depicting intense Tc-99m (V) DMSA uptake (i.e. equal to or greater than nasopharyngeal activity) on scintiscans at the sites corresponding to palpable cervical lymph nodes, the most likely diagnosis was mycobacterial lymphadenitis (Figs 2, 3).

In the lymphoma patients (Hodgkin and non-Hodgkin) there was not any increase in the uptake of the radiotracer by the lymph nodes. In the patient with branchial cyst, the mass demonstrated a photopenic appearance (complete absence of activity) an anticipated findings consistent with its cystic nature (Fig 4).

Table I- Histopathological distribution of the cases

Benign Lesions	
Branchial Cyst	: 1
Tuberculous Lymphadenitis	: 5
Reactive Lymphadenitis	: 8
Angiofollicular Lymphoid Hyperplasia	: 1
Schwannoma	: 1
Chronic Abscess Infection	: 1
Malign Lesions	
Hodgkin Lymphoma	: 1
Non-Hodgkin Lymphoma	: 1
Nasopharynx Cancer Metastasis	: 1
TOTAL	**: 20**

Table II- The Characteristics of the Patients and the Uptake

NAME	SEX	AGE	LOCALIZATION	US SIZE (mm)	DIAGNOSIS	PPD (mm)	DMSA
Y.C.	M	55	Subauriculary (R)	30 x 20	Reactive LAP	8	+
H.T.	M	21	Submandibulary (R)	11 x 16	Reactive LAP	5	+
T.A.	M	20	Angle of the Mandible (R)	10 x 10	Reactive LAP	3	+
Ç.D.	M	18	Sub. Jugulary (R)	20 x 10	Reactive LAP	5	-
M.O.	M	25	Bilateral Cervical Region	20 x 10	Reactive LAP	10	+
A.A.	M	24	Submandibulary (L)	10 x 15	Reactive LAP	5	+
İ.T.	M	21	Post. of Mandibular Ramus (R)	21 x 11	Reactive LAP	8	+
A.Y.	M	41	Post. Lymphatic Chain (L)	16 x 10	Reactive LAP	12	+
E.K.	M	20	Middle Cervical (L)	15 x 15	Tbc Adenitis	21	++
Ş.Y.	M	20	Sub Parotic (L)	16 x 10	Tbc Adenitis	24	+
A.A.	M	40	Sub Parotic (L)	45 x 25	Tbc Adenitis	22	++
M.T.	M	21	Bilateral Cervical	47 x 42	Tbc Adenitis	21	++
S.G.	M	22	Angle of the Mandible (R)	20 x 20	Tbc Adenitis	22	++
Z.Ç.	M	20	Anterior Cervical (L)	80 x 50	Hodgkin	5	-
Y.O.	M	23	Sub Parotic (L)	20 x 20	Non-Hodgkin	8	-
A.K.	F	25	Sub Parotic (L)	27 x 21	Schwannoma	26	++
O.H.	F	59	Ant. of SCM (L)	40 x 40	Branchial Cyst	21	-
M.K.	M	21	Submandibulary (L)	18 x 9	Chronic Absc. Infection	22	++
M.O.	M	38	Inf. of SCM (R)	14 x 10	Nasoph. Ca Metastasis	10	++
D.O	M	19	Anterior Cervical Region (R)	20 x 20	Angiofol. Lymp. Hyperplasia	8	+

DMSA Uptake : No uptake : –
Minimal uptake : +
Equal uptake with nasopharynx or more : ++
US : Ultrasonography
DMSA : Intensity on pentavalent DMSA scintigraphy
SCM : Sternocleidomastoid muscle

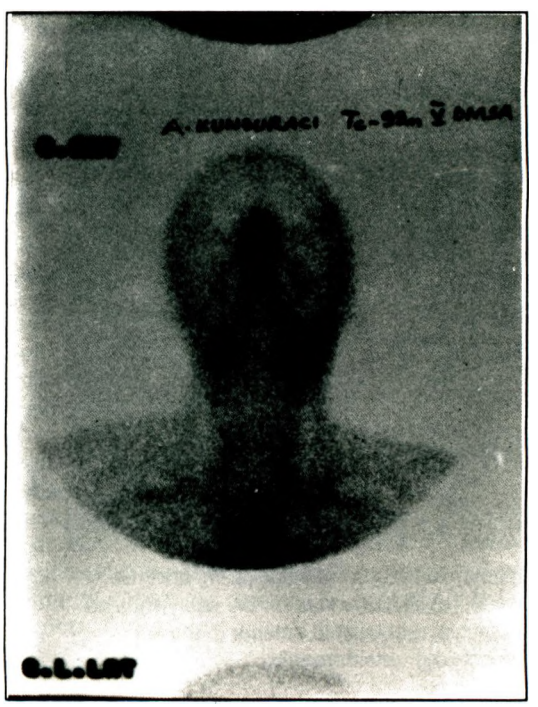

Fig 1. Intense uptake of Tc-99m (V) DMSA is seen on scintigraphy at the site of the palpable mass under the left parotid gland that measured 27x21 mm ultrasonographically. A diagnosis of Schwannoma was established by histopathological examination of biopsy material.

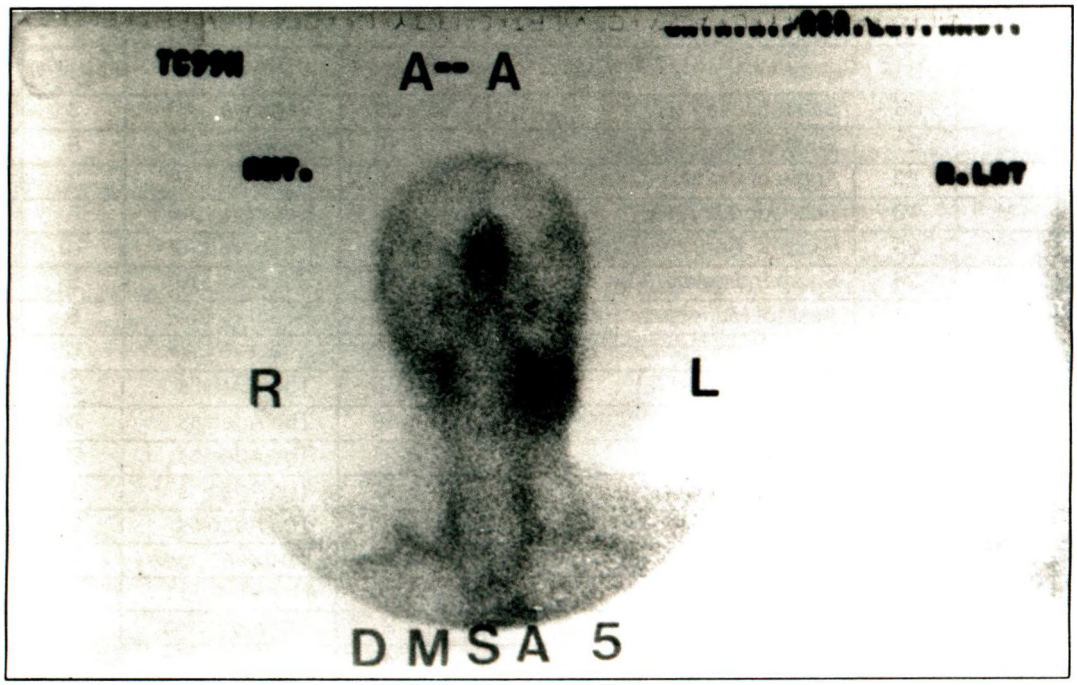

Fig 2. An intense uptake of pentavalent DMSA that is greater than the nasopharyngeal activity is depicted scintigraphically in the patient with a 45 x 25 mm cervical lymph node located inferior to the left parotid gland. The diagnosis of tuberculous lymphadenitis was established clinically and histopathologically.

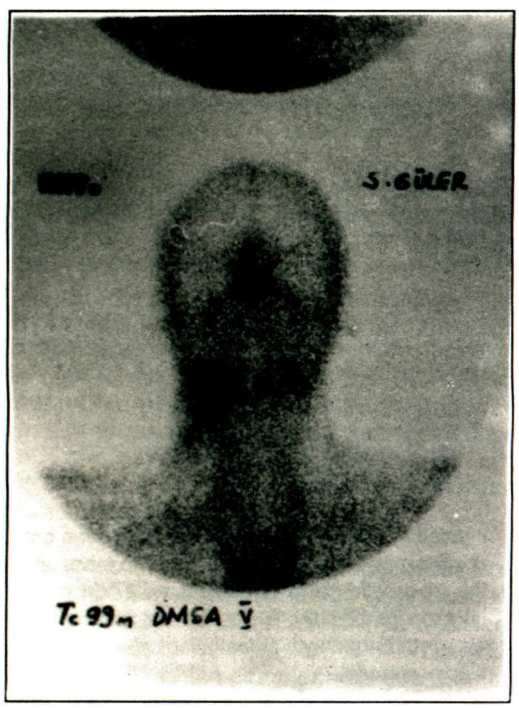

Fig 3. Accumulation of Tc-99m (V) DMSA on scintigraphy corresponds to the palpable adenopathy beneath the left mandibular angle that was diagnosed as tuberculous adenitis later on.

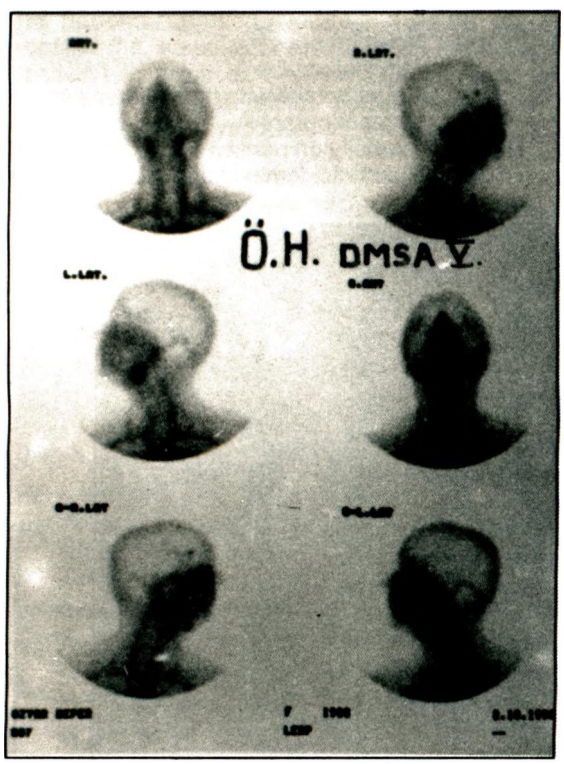

Fig 4. A photopenic region demonstrating absence of Tc-99m (V) DMSA is seen in the case who had a branchial cyst located anterior to the left sternocleidomastoid muscle.

DISCUSSION

Tc-99m (V) DMSA is reported to have a dual imaging character: a bone seeking property and a tumor seeking property. It is avidly accumulated by medullary thyroid carcinoma and its metastases.

The postulated uptake mechanism in medullary thyroid cancer requires the presence of the dissociated TcO_4^{-3} anion in the pentavalent DMSA. This anion seems to be a metabolic mimic of phosphate which has been shown to be taken up by neoplasms possibly as a consequence of calcification (4). The assumed structural similarity of Tc-99m (V) DMSA (i.e. TcO_4^{-3}) and (PO_4^{-3}) was tested by Ohta et al. in their investigation for the anticipated accumulation of the agent in patients with lung metastases of osteosarcoma. They demonstrated adequate accumulation of Tc-99m (V) DMSA by emission computed tomography (ECT) imaging (5). Ohta and his coworkers also demonstrated significant uptake of the radiotracer at the sites of amyloid deposition (6). The affinity of bone seeking Tc-99m-labeled phosphates to amyloid has been documented previously. At the present time, imaging with a bone seeking agent, especially, technetium-99m pyrophosphate (^{99m} Tc-PYP) is the most widely used nuclear medicine technique to detect amyloidosis (7).

Clarke et al. compared pentavalent (Tc-99m) DMSA, 1-131 MIBG and Tc-99m-MDP in patients with medullary carcinoma of the thyroid, regarding lesion detection (8). They reported that Tc-99m (V) DMSA demonstrated uptake in significantly more lesions with better detectability of both soft tissue and bony metastases. Their observation that Tc-99m (V) DMSA depicts uptake in more sites as compared to Tc-99m-MDP suggests that the structural analogy with phosphate ion may not the only explanation of the tumor-seeking property of pentavalent DMSA. Blower et al. reported that of three stereoisomers coexist in pentavalent DMSA and all three isomers are significant components of the radiopharmaceutical (9).

The observation in this study that pentavalent DMSA is taken up by the lymph nodes infected by mycobacterium tuberculosis with subsequent caseation is consistent with the postulation of Ohta based on structural similarity with the phosphate ion. It is tempting to speculate that the coexistance of three isomers may account for the simultaneous bone and tumor-seeking properties of pentavalent DMSA. Some of these isomers may have affinity to bone/calcium whereas other (s) may have affinity for tumor. This may explain the reason for uptake both in nonneoplastic conditions such as amyloidosis and tuberculous lymphadenitis and in neoplasms. Further investigations regarding the in vivo behavior of individual isomers is warranted to clarify the localization mechanism and the diagnostic value (in terms of sensitivity, specificity, accuracy etc.) of each isomer.

Tuberculous lymphadenitis is more common in young adults. In the patients with tuberculous adenitis, the order of involvement of lymph nodes is as follows: the anterior and posterior cervical nodes (in more than 50%), the supraclavicular (in about 20%), the submandibular, axillary, subauricular and other nodes.

Mycobacteria-infected lymph nodes (lymphadenitis) are commonly located in the neck region (cervical lymphadenitis). The differential diagnosis between nontuberculous and tuberculous mycobacteria is essential since their managements are very different. The differential diagnosis can be done clinically, by tuberculin skin testing and by culture of lymph node biopsy material.

Clinically our patient group is more likely to have tuberculous rather than nontuberculous mycobacterial lymphadenitis because of the following criteria: Their age group (presently tuberculous lymphadenopathy occurs in adults 20 to 40 years of age), the presence of multiple nodes within a group (together with bilateral involvement in one case) and the absence of chronic draining ulcers. In the United States, M. tuberculosis is the most important causative agent in adult patients with mycobacterial cervical lymphadenitis with only 5% of isolates being atypical mycobacteria (i.e. mycobacteria other than tuberculosis) (10, 11). In contrast, in children the most frequent cause of mycobacterial cervical lymphadenitis is reported as atypical mycobacteria (12). The most meaningful finding was the very intense skin test reaction (induration equal to or greater than 20 mm) observed in all of the four patients, which suggests tuberculosis rather than mycobacteria other than tuberculosis (MOTT) infection. In most geographic regions, using 15 mm induration reaction as the cutoff point in interpreting the Mantoux test will best identify M. tuberculosis infection (13). The culture of lymph node biopsy material is necessary not only to confirm the presence of mycobacteria, but also to establish the etiologic diagnosis of cervical lymphadenitis. A definite diagnosis of MOTT lymphadenitis is made by recovery of the causative organism from lymph node cultures. However, in most series, only about one half of excised infected lymph nodes will be culture-positive (14). Because of technical problems lymph node cultures could not be obtained on a routine basis in this study. However, the histopathological diagnosis of tuberculous lymphadenitis with presence of caseous necrosis in all of the 4 patients and the favorable response of these patients to antituberculous chemotherapy during the follow-up, together with very intense PPD reaction and other clinical characteristics resulted in the clinical diagnosis of tuberculous lymphadenitis.

If an intense uptake of Tc-99m DMSA is accompanied by a tuberculin skin testing result of very intense reaction (20 mm or more induration) in a patient with high-risk epidemiologic profile and/or histopathology consistent with mycobacterial lymphadenitis (15); it seems appropriate to

commense antituberculous chemotherapy to save time while waiting for cultures. If the culture is positive for MOTT, then the therapy may be stopped (15).

This study was designed to investigate the role of Tc-99m (V) DMSA scintigraphy in the initial work-up of patients with cervical lymphadenopathy. It turned out that pentavalent DMSA scintigraphy may have the potential to suggest or to rule out the possibility of mycobacterial lymphadenitis. This preliminary finding needs to be further investigated in larger series consisting of patients with tuberculous and MOTT lymphadenitis and their control groups.

In the present study, the role of pentavalent DMSA scintigraphy as a first line procedure in the work-up of patients with cervical lymphadenopathy was investigated. The reactive cervical lymphadenopathies that responded to antibiotherapy later on, demonstrated faint uptake on scintigraphy performed before the final diagnosis was established and the appropriate therapy was initialized. Patients who turned out to have mycobacterial lymphadenitis (evaluated as tuberculous lymphadenitis on clinical, histopathological grounds and because of very intense tuberculin skin test reactions) showed intense accumulation of pentavelent DMSA in the affected lymph nodes.

The intense uptake of Tc-99m (V) DMSA in tuberculous lymphadenitis seems to be secondary to the presence of calcium in this lesion. This is consistent with the structural similarity of pentavalent DMSA with the phosphate ion as proposed by Ohta. The anticipated affinity of calcium, that is precipitating at sites of caseous necrosis, for phosphate-like pentavalent DMSA was observed in our limited subgroup of patients with tuberculous lymphadenitis. Since the presence of three stereoisomeres of pentavalent DMSA are reported, it is tempting to speculate that the above-mentioned property (i.e. the affinity for caseating tuberculosis) is attributable to a stereoisomer that is not responsible for the known tumor affinity of the radiopharmaceutical. Further investigation of the validity of these preliminary findings (regarding mycobacterial lymphadenitis) in larger patient series and for each stereoisomer of pentavalent DMSA is warranted.

Imaging of cervical lymph nodes via DMSA scintigraphy is a non-invasive cheap, safe and simple diagnostic procedure. It may be used on a routine basis to assist in the differential diagnosis of patients with cervical lymphadenopathies. It was found to be useful to predict reactive adenitis in the biopsy-proven suspicious cases. Likewise, pentavalent DMSA is accumulated in mycobacteria-infected lymph nodes with caseating necrosis.

A single study cannot be expected to precisely predict all diagnoses in the work-up of cervical lymphadenopathies. Therefore pentavalent DMSA scintigraphy should be considered an important complement to, rather than a replacement for, conventional histopathological and bacteriological (recovery of the causative organism from lymph node cultures) evaluation of the lymph nodes. But it should also be born in mind that an intense uptake of pentavalent DMSA in cervical lymph nodes accompanied by a very intense tuberculin skin test reaction may lead to the initiation of antituberculous chemotherapy in high-risk patients instead of waiting for the results of special culture results that take long time.

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