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Cervical lymphadenopathy due to mycobacterial infection: a diagnostic protocol

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Abstract
Mycobacterial cervical lymphadenopathy is relatively uncommon in the United Kingdom; when cases do occur opportunities for early diagnosis and treatment may be missed. We have reviewed twenty-three cases of mycobacterial cervical lymphadenopathy presenting to an urban general hospital over a four-year period. We discuss the techniques available to aid a diagnosis of mycobacterial disease and suggest a protocol to allow efficient use of these techniques.

Key words: Lymphadenitis, cervical; *Mycobacterium tuberculosis*

Introduction

The superficial lymph nodes in the neck represent one of the major sites of non-respiratory tuberculosis (Medical Research Council, 1980). The majority of cases are caused by *Mycobacterium tuberculosis*. *Mycobacterium bovis*, which in 1956 accounted for half of all cases within the U.K. is now very unusual. Atypical mycobacterial infections are also seen in the U.K., especially in children, but are much less common.

Patients with cervical mycobacterial infections often present with a lump in the neck. The route of entry is thought to be via the upper aerodigestive tract but in up to 60 per cent of patients no primary focus of infection is found (Lau *et al.* 1991). Patients may be referred to otolaryngology, general surgical or general medical clinics. Because of this heterogeneity of referral patterns there is a wide variation in the investigations used and the time taken to reach a diagnosis. We have reviewed all the cases of cervical mycobacterial infection in an urban general hospital over a four-year period and suggest a protocol for investigating such patients.

Methods

The case records of all patients in the register of notifications of *Mycobacterium tuberculosis* at Barnet General Hospital over a four-year period were reviewed and patients with cervical tuberculosis were identified. This information was checked against records held by the microbiology department and patients with atypical mycobacterial infection were also identified from these records.

Results

Twenty adults and three children were identified with cervical mycobacterial infections. All the adults had been born abroad (Fig. 1) and had lived in the U.K. for an average of 13.8 years (range 7 months to 60 years). Their mean age was 44 years (range 22–88 years) and there were equal numbers of men and women. Seven had a first degree relative who had had tuberculosis within the past 10 years and another had had pulmonary tuberculosis 14 years previously. The three children were all three-year old girls born in the U.K. and had parents who had always lived in the U.K.

All patients presented with neck symptoms and signs. Three had a cervical sinus at presentation and the others had a lump in the neck. The mean duration between first noticing the problem and the first outpatient attendance was three months (range two weeks to one year). Seven

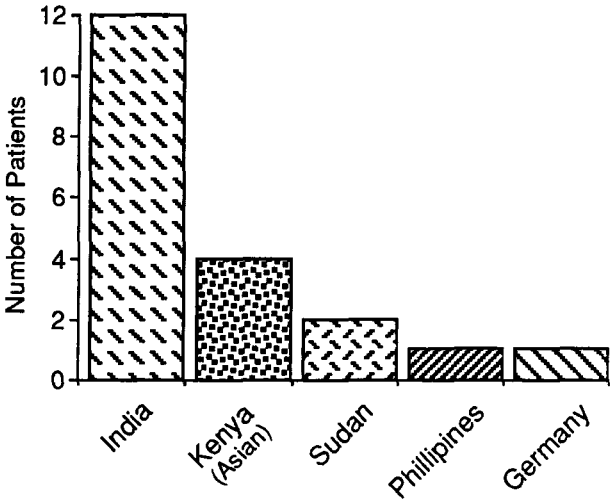

FIG. 1
Country of origin of adult patients.

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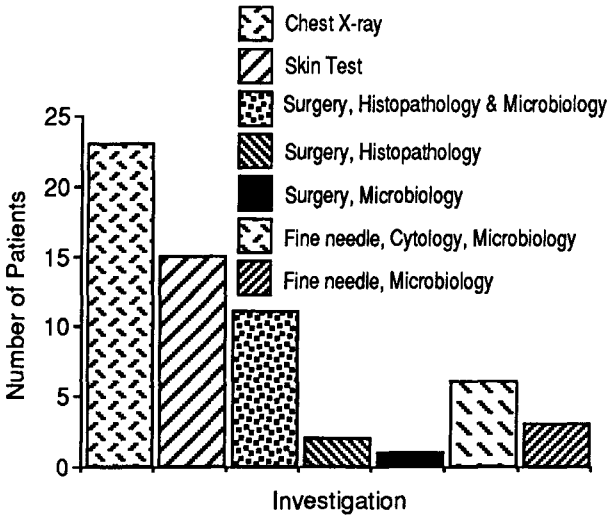

FIG. 2
Investigations performed.

adults had other symptoms including night sweats and weight loss.

The patients presented to a number of different specialities and there was considerable variation in the investigations used to make the diagnosis (Fig. 2).

Fifteen patients had either Mantoux or Heaf skin tests. There was a strongly positive reaction in 12 patients, an equivocal reaction in two and no reaction in one patient who was later found to have miliary tuberculosis.

Nine patients underwent fine needle aspiration of the neck mass. In six cases the aspirate was sent for both cytopathology and microbiology and in the other three it was sent to microbiology alone. The cytology showed granulomatous inflammation in one case and in the other cases, although not suggestive of mycobacterial infection, did help to rule out a malignant cause for the mass. Staining of the specimens sent to microbiology was positive for acid-fast bacilli in two cases. The specimens were cultured for six weeks in Lowenstein-Jensen medium and *Mycobacterium tuberculosis* was grown in eight cases.

Surgical exploration of the neck was undertaken in 14 patients. Samples were sent to histopathology in 13 cases. Acid-fast bacilli were seen in one case, granulomatous inflammation in 10, simple chronic inflammation in one and acute inflammation in the final specimen. Twelve samples were sent to microbiology. Acid-fast bacilli were seen in three stained samples and mycobacteria were grown in all twelve cases. Two of these were from children and grew *M. Kansasii* and *M. avium intracellulare* respectively. The specimen from the third child was not sent for mycobacterial culture.

All the patients had a chest X-ray. This was normal in 19 patients and suggestive of active pulmonary tuberculosis in four cases.

Medical treatment was started as soon as a provisional diagnosis was made and before culture results were available. Fig. 3 shows the most reliable positive investigation in each case which led to the provisional diagnosis of mycobacterial infection and Fig. 4 shows the basis for the final diagnosis.

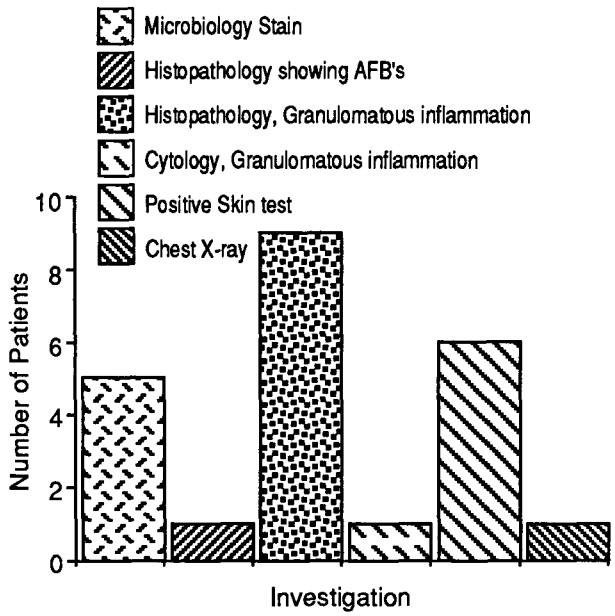

FIG. 3
Most reliable positive investigation for provisional diagnosis.

Discussion

The least invasive investigation for diagnosing *M. tuberculosis* infection is tuberculin skin testing. Several methods are available including the Mantoux, Heaf, imotest and tine tests. The Mantoux is the oldest and is still probably the most reliable of these. Five tuberculin units are injected intracutaneously and the subsequent delayed hypersensitivity skin reaction is assessed at between 48 and 72 hours. In most patients a reaction of 10 mm or greater is considered positive. In immunosuppressed patients a 5 mm reaction suggests active infection. The Heaf, imotest and tine tests use a multiple puncture technique to introduce tuberculin and are less accurate. They are used for large scale screening programmes because they are much faster than the Mantoux test (Anand and Roberts, 1991).

Cross-reactivity can occur in patients who have been exposed to atypical mycobacteria and false negatives occur, particularly in immunosuppressed patients (American Thoracic Society, 1990). In pulmonary tuberculosis false negative results may occur in up to 25 per cent of cases (Nash and Douglas, 1980). Thus, whilst skin testing is often helpful in making a provisional diagnosis,

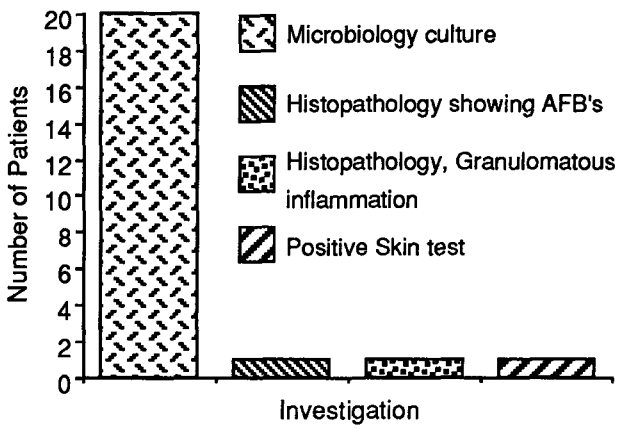

FIG. 4
Most reliable positive investigation for final diagnosis.

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the results of this investigation must be treated with caution.

Fine needle aspiration cytology is a quick and minimally invasive investigation allowing samples to be obtained for cytopathology and microbiology. When used in cervical *M. tuberculosis* infections it has a sensitivity of around 80 per cent and specificity of 93 per cent (Dandapat *et al.* 1990; Lau *et al.*, 1990). Even if a diagnosis of tuberculosis cannot be reached on the basis of the cytology other diagnoses, including malignancy, can be excluded. The material obtained for microbiological investigation may still allow a diagnosis to be made following a direct smear and subsequent culture (Rajwanshi *et al.*, 1987; Lau *et al.*, 1990; Brown and Coghill, 1992).

Surgical exploration and incisional or excisional biopsy of the affected node provides ample material for both microbiology and histopathology. (Lau *et al.*, 1990). It has been suggested that surgical exploration should be carried out as the primary diagnostic investigation following clinical examination (Shikani *et al.*, 1989). Surgical exploration is invasive and carries a risk of damage to adjacent structures and, especially with *M. tuberculosis*, a risk of persistent post-operative fistulae.

Histopathological examination of tuberculous lymph nodes can usually demonstrate caseating or non-caseating granulomatous inflammation. However, even when specific stains for acid-fast bacilli are used, tubercle bacilli are often not seen (Betts and Reese, 1986). The differential diagnosis of granulomatous inflammation includes sarcoidosis, brucellosis, cat-scratch fever, leprosy, some mycotic infections and foreign body reactions (Robbins, 1984).

Microbiological examination of specimens consists of a smear using stains for acid-fast bacilli and culture in a suitable growth medium. Staining techniques include the conventional acid-fast stains (e.g. Ziehl-Neelsen) and the fluorochrome procedure using stains such as auramine and rhodamine (American Thoracic Society, 1990). When smears are performed on fine needle aspirates of tuberculous nodes around 60 per cent will stain positive (Metre and Jayaram, 1987; Arora and Arora, 1990).

Conventional culture techniques use Lowenstein-Jensen or similar culture media. Positive cultures often take four to six weeks and are rarely available before three weeks. Cultures are obtained in 30 to 90 per cent of cases. Specimens obtained by surgical exploration are most likely to be positive. Lymph nodes with caseous necrosis are more likely to yield a positive culture than those without necrosis (Radhika *et al.*, 1989; Arora and Arora, 1990; Lau *et al.*, 1991).

New techniques to allow more rapid detection and identification of pathogenic mycobacteria by combining radiometric methodology and nucleic acid probe methods have been developed in the United States (Ellner *et al.*, 1988) and elsewhere but are not yet routinely available in the U.K.

A chest X-ray should always be requested in patients with persistent cervical lymphadenopathy but, because most patients have a normal result, it cannot be relied upon to diagnose the cause of the lymphadenopathy in the majority of cases.

It is unfortunate that none of the conventional investigations described here offer an immediate confirmation of the diagnosis of mycobacterial infection with high specificity and sensitivity. However a combination of investigations can lead to a very high suspicion of mycobacterial infection whilst virtually ruling out malignant lymphadenopathy. Appropriate treatment can then begin whilst the results of cultures are awaited.

Whilst any diagnostic protocol has to be flexible enough to take account of different presentations it must also prevent the omission of important investigations. In the study presented here samples of surgical specimens were not always sent to microbiology and, when they were, mycobacterial stains and cultures were not always requested.

We suggest the following protocol should be followed in all cases. Any patient who presents with a node in the neck should have a full history recorded and a clinical examination including mirror or fibreoptic examination of the post-nasal space and larynx. All patients should have a full blood count, erythrocyte sedimentation rate, chest X-ray and fine needle aspiration cytology of the node with specimens being sent to cytopathology and microbiology. The possibility of tuberculosis should be mentioned on the microbiology request form. Patients who come from a high risk population for tuberculosis or in whom the history suggests tuberculosis should have a Mantoux test in addition to these investigations. A Mantoux test should also be performed on those low risk patients in whom the initial investigations point to a possible diagnosis of tuberculosis.

If acid-fast bacilli are seen on cytology staining or on a microbiology smear stain a diagnosis of tuberculosis can be assumed and appropriate treatment started whilst cultures are awaited. It is probably acceptable to make a presumptive diagnosis on the basis of a positive skin test coupled with a fine needle result showing granulomatous inflammation. In those cases where these criteria are not fulfilled arrangements should be made to admit the patient for panendoscopy and incisional or excisional biopsy of the node. Material should be sent for both histopathology and microbiology. Tuberculous nodes do not always have the 'typical' matted appearance mentioned in most textbooks and in several cases in this study tuberculous infection had not been suspected prior to biopsy because of the discreet nature of the lymphadenopathy.

If a similar protocol to this had been followed in the patients audited here unnecessary surgery and delays in diagnosis could have been avoided without compromising the early diagnosis of other causes of cervical lymphadenopathy.

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