Transbronchial lung biopsy through fibreoptic bronchoscope in diagnosis of sarcoidosis

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Summary and conclusions

Sarcoidosis was ultimately diagnosed in a consecutive series of 79 patients, of whom 24 presented with unusual features. Histological support for this diagnosis was obtained in 37 out of 42 patients who underwent transbronchial biopsy; epithelioid and giant-cell granulomas were also found on biopsy of the bronchial mucosa in 17 out of 22 patients. Kveim tests were completed in 44 patients: results were positive in 19, equivocal in 11, and negative in 14. In 16 patients histological support was obtained on biopsy of various other tissues. The clinical presentation of the disease and the degree of histological support provided by the various procedures used in reaching a diagnosis of sarcoidosis varied considerably.

Transbronchial biopsy of the lung is a useful advance in diagnosing sarcoidosis and provided a higher diagnostic yield than any other method.

Introduction

Although sarcoidosis is fairly common with diverse clinical manifestations, abnormalities on the chest radiograph are usually observed during its course or first suggest the diagnosis in asymptomatic patients. A recent and important advance in diagnosing sarcoidosis has been the use of fibreoptic bronchoscopy to obtain biopsy tissue from the bronchial mucosa or adjacent lung. We report here our findings using this procedure and compare them with the results obtained using other diagnostic techniques in investigating a highly selected group of 79 consecutive patients seen at this hospital between January 1977 and December 1978 in whom sarcoidosis was diagnosed.

Patients and methods

We investigated 79 patients (40 men, 39 women). Sarcoidosis was highly probable in 55, based on the usual radiological classification: in one the chest radiograph was normal; 12 had bilateral hilar lymphadenopathy; 36 had bilateral hilar lymphadenopathy and pulmonary mottling; and six had pulmonary mottling alone. In eight patients a disease other than sarcoidosis was provisionally diagnosed: pulmonary tuberculosis (three); systemic lupus erythematosus (one); cryptogenic fibrosing alveolitis (one); honeycomb lung (one); budgerigar lung (one); and Hodgkin's disease (one). No diagnosis had been reached in the 16 remaining patients, who showed the following clinical abnormalities: diffuse bilateral pulmonary shadows (nine); diffuse bilateral pulmonary mottling and pericarditis (two); enlarged cervical lymph nodes and asymmetric hilar lymphadenopathy (two); diffuse upper-zone shadow (two); and pleural effusion (one).

Lung biopsy specimens were obtained transbronchially under fluoroscopic control[1] in 42 patients: four to eight specimens were taken in each case. In some patients specimens from the bronchial mucosa were also taken during the procedure; while in some patients only biopsy of the bronchial mucosa was carried out. Tissue from various other sites was obtained in a few patients (see table I).

Kveim tests were performed in 44 patients by giving intracutaneously 0·15 ml of a test suspension prepared from spleen K19. A punch biopsy of the test site was carried out four weeks after injection.[2]

All tissues were fixed in 10% formol saline; serial sections were prepared and stained with haematoxylin and eosin, Ziehl-Neelsen, and Grocott stains.

TABLE I—*Methods used to obtain histological support for diagnosis of sarcoidosis in 73 patients*

Method	No of patients	Result		
		Positive*	Equivocal	Negative
Transbronchial biopsy	42	37		5
Biopsy of bronchial mucosa	22	17		5
Kveim test	44	19	11	14
Biopsy of cervical lymph node	10	10		
Biopsy of skin lesion	1	1		
Liver biopsy	2	2		
Biopsy of mediastinal lymph node	2	2		
Biopsy of enlarged parotid gland	1	1		

*Epithelioid and giant-cell granulomas present.

Results

Histological support for a diagnosis of sarcoidosis was ultimately obtained in 73 of the 79 patients (table I). In all cases the subsequent evolution of disease with or without treatment over a follow-up period ranging from nine to 33 months remained compatible with this diagnosis, and no alternative diagnoses emerged. We therefore present the findings in all 79 patients.

Fibreoptic bronchoscopy was performed in 50 patients: endobronchial lesions (plaques or bronchial stenoses) compatible with sarcoidosis were visible in 19 and minor abnormalities of the bronchial mucosa in 13; the remaining 18 showed normal appearances. Tables I and II show the methods used to obtain histological support for a diagnosis of sarcoidosis and the results obtained in relation to the appearances on the chest radiograph. Transbronchial biopsy was undertaken in 42 patients: 37 (88%) showed the presence of epithelioid and giant-cell granulomas in the lung. Biopsy of the bronchial mucosa was performed in 22 patients (a few of whom also underwent transbronchial biopsy); 17 specimens (77%) showed epithelioid and giant-cell granulomas. Kveim tests were completed in 44 patients: 19 results (43%) were positive, 11 equivocal, and the remaining 14 negative. Table III compares the biopsy findings and the results of Kveim tests in 29 patients investigated by both procedures. In 24 patients transbronchial biopsy or biopsy of the bronchial mucosa showed the presence of epithelioid and giant-cell granulomas: results of Kveim tests were positive in 11 cases, equivocal in three, and negative in 10. The remaining five patients showed no histological evidence of disease: results of Kveim tests were positive in two, equivocal in one, and negative in two. In addition (table I), epithelioid and giant-cell granulomas were shown on biopsy of other tissues in 16 patients.

Discussion

Of the 79 patients studied, in all of whom sarcoidosis was ultimately diagnosed, 15 (19%) had an abnormal chest radiograph that did not fit the conventional radiological classifi-

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TABLE II—*Results of biopsy of bronchial mucosa, transbronchial biopsy, and Kveim tests in all 79 patients*

Chest radiographic appearances	No of patients	Biopsy of bronchial mucosa		Transbronchial biopsy			Kveim test		
		No examined	No positive*	No examined	No positive*	% positive	No tested	No positive*†	% positive
Normal	1	0		0			1	1	
Hilar lymphadenopathy	12	1	0	3	2	66	12	7 (2)	58
Hilar lymphadenopathy and pulmonary mottling	37	16	12	23	19	83	22	8 (6)	36
Pulmonary mottling only	16	3	3	11	11	100	6	3 (2)	50
Pulmonary fibrosis	3	0		3	3	100	2	0	0
Other	10	2	2	2	2	100	1	0 (1)	0
Total	79	22	17 (77%)	42	37	88	44	19	43

*Epithelioid and giant-cell granulomas present.
†Figures in parentheses indicate numbers of equivocal responses to Kveim test.

TABLE III—*Comparison of results of transbronchial biopsy or biopsy of bronchial mucosa, or both, and results of Kveim tests in 29 patients investigated by both procedures**

Kveim test	Biopsy		Total
	Positive†	Negative	
Positive	11	2	13
Equivocal	3	1	4
Negative	10	2	12
Total	24	5	29

*Transbronchial lung biopsy and Kveim test carried out in 21 patients; biopsy of bronchial mucosa and Kveim test carried out in eight patients.
†Epithelioid and giant-cell granulomas present.

cation of pulmonary sarcoidosis.[3] Unusual chest radiographic appearances are recognised in sarcoidosis and may take the form of widespread bilateral conglomerate shadows or, more rarely, localised shadows in the upper part of one lung.[4] In two patients in this series hilar lymphadenopathy was predominantly unilateral: this is a recognised feature in 1-3% of patients with sarcoidosis who present with hilar or paratracheal lymphadenopathy, or both.[5] One patient presented with a pleural effusion; although uncommon, granulomatous disease of the pleura with or without pleural effusion may occur in sarcoidosis.[6] Fifty-five patients were thought to have sarcoidosis on clinical grounds, and biopsy was performed to confirm the diagnosis; whereas in the remaining 24 (32%) the disease was undiagnosed or misdiagnosed and biopsy was required to obtain a diagnosis.

Epithelioid and giant-cell granulomas were found on biopsy of a cervical lymph node in 10 patients and of the skin in one. Peripheral lymph nodes may be palpable at some time in almost all cases,[7 8] and it is therefore important to search for enlarged peripheral lymph nodes, subcutaneous swellings, or skin lesions, as biopsy of these may provide histological support for the diagnosis.

The Kveim tests were carried out with batches of the splenic suspension K19. Studies in 3290 patients[2] have shown that K19 yields a distribution of Kveim reactivity closely in keeping with that reported previously[9 10]; and it has the qualities associated with validated Kveim test suspensions.[11] Overall, under half the patients tested reacted to the suspension, and fewer reactions than would be expected occurred in patients with stage 2 disease (hilar lymphadenopathy and pulmonary mottling). This may partly be due to the well-recognised waning in Kveim reactivity among patients with sarcoidosis of more than two years' duration.[2 10]

Transbronchial biopsy through a fibreoptic bronchoscope has a low complication rate[12] and is comfortable for the patient. General anaesthetic is not required. The specimens obtained are small, but special fixation techniques[13] permit accurate histological diagnosis in most cases. In the present series 37 (88%) out of 42 patients investigated by transbronchial lung biopsy showed evidence of disease. Granulomas were present in the lung specimens from all 14 patients with pulmonary mottling only or pulmonary fibrosis (stages 3 and 4) and also in specimens from two out of three patients with hilar lymphadenopathy only (stage 1). Although the rate of positive findings on transbronchial biopsy is high among patients with sarcoidosis who have radiological evidence of pulmonary infiltration, it is also high (abqut 60%) among patients with hilar lymphadenopathy whose chest radiographs show normal lungfields.[14 15] Interestingly, out of 22 patients in the present study who underwent biopsy of the bronchial mucosa, 17 (77%) had granulomas; and the bronchial mucosa often showed remarkably little scarring, even in patients with chronic pulmonary sarcoidosis associated with pulmonary fibrosis.[16]

In two patients granulomas were present in tissue from mediastinal lymph nodes obtained by mediastinoscopy. Taken alone this finding does not confirm the diagnosis of sarcoidosis, since it may also occur in tuberculosis, lymphoma or other malignant disease, berylliosis, brucellosis, extrinsic allergic alveolitis, histoplasmosis, collagen disorders, and antibody deficiency syndromes.[17–19] Clinical and radiographic features, however, usually make the distinction obvious. In two patients epithelioid and giant-cell granulomas were found on liver biopsy: miliary granulomas are present in the liver in about two-thirds of all patients with sarcoidosis, but only a few patients with hepatic granulomatosis have sarcoidosis.[20]

In this study we placed emphasis on tissue biopsy methods and the Kveim skin test. Nevertheless, a "blind" conjunctival biopsy will show granulomas in one-third of patients with sarcoidosis,[21] and indirect methods such as gallium scanning, assaying fluid obtained by bronchial lavage, and measuring serum concentrations of angiotensin-I-converting enzyme may provide additional support for the diagnosis.[22–24]

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(*Accepted 2 January 1980*)

Successful treatment of experimental B virus (Herpesvirus simiae) infection with acyclovir

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Summary and conclusions

The efficacy of the new nucleoside analogue acyclovir against B virus (Herpesvirus simiae) was investigated in rabbits and Vero cells infected with 2-136 and 0·3-1·0 TCD_{50} of the virus respectively.

In the Vero cells 1 mg of acyclovir/l reduced the yield of virus by 90%, which was slightly less than the effect on herpes simplex virus. Results in the rabbits varied with the interval between doses, duration of treatment, and delay before starting treatment. Acyclovir controlled an otherwise lethal infection when given not less than eight-hourly for 14 days. Withdrawing treatment after 9-10 days resulted in late-onset fatal disease in some rabbits. Treatment begun within 24 hours after infection gave complete protection, and rabbits first treated up to five days after infection showed a significant reduction in mortality ($p < 0·001$).

The plasma half life of acyclovir is twice as long in man as in rabbits and progression of the disease is much slower. Hence acyclovir may be useful for post-exposure prophylaxis against B virus infection in man and possibly also for treatment of the disease.

Introduction

Infection with B virus (*Herpesvirus simiae*) resulting from contact with macaque monkeys or their tissues rarely occurs but is almost invariably fatal; out of 24 reported cases, only one patient made a reasonable recovery,[1] though three others survived with severe neurological sequelae. The Medical Research Council has therefore established a special unit at the Microbiological Research Establishment to investigate the disease, including possible approaches to prophylaxis and treatment. Several antiviral agents have been tested both in vitro and in vivo. For the in-vivo studies rabbits have been used; rabbits respond to subcutaneous injection of small amounts of virus with a fatal ascending encephalomyelitis that is closely similar to the disease in man after a bite from an infected monkey. Adenine arabinoside (vidarabine) was the most active antiviral compound in early in-vitro tests, but pronounced depression of viral replication occurred only with high concentrations of the drug. Thus, as expected, vidarabine had little effect on mortality in rabbits infected with B virus, though survival was prolonged if treatment was begun immediately after infection.

The new nucleoside analogue acyclovir (acycloguanosine; 9-(2-hydroxyethoxymethyl) guanine; Burroughs Wellcome Co) is highly active against several herpesviruses both in vitro and in various animals.[2-6] It was also effective in human corneal ulcers caused by herpes simplex virus[7] and in pneumonia that developed in an immunocompromised boy a few days after the onset of severe and extensive herpes labialis.[8] We describe experiments suggesting that acyclovir will be useful in post-exposure prophylaxis against B virus infection in man and possibly for treating clinically evident disease.

Materials and methods

All manipulation of materials infected with B virus was carried out in completely enclosed class III safety cabinets. Culture flasks and other apparatus were disinfected by swabbing with 2% sodium hypochlorite solution (Chloros) before removal from the cabinet for incubation or other procedures. Culture medium was buffered with HEPES (N-2-hydroxyethylpiperazine-N¹-2-ethanesulphonate) to avoid the need to flush cultures with carbon dioxide.

Yield-reduction test—Confluent monolayers of Vero cells in 25 cm^2 plastic flasks were infected with 0·3-1·0 TCD_{50} of B virus/cell. The infected monolayers were washed and covered with 3 ml of medium containing appropriate concentrations of antiviral compound. After

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