Eur Respir J 2005; 26: 989–992
DOI: 10.1183/09031936.05.00027505

Autofluorescence videothoracoscopy in exudative pleural effusions: preliminary results

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ABSTRACT: Videothoracoscopy has been proven to be a safe tool to establish the diagnosis in >90% of patients with exudative pleural effusions of unknown origin. In the majority of patients with malignant pleural diseases, the endoscopic appearance of pleural lesions during white light thoracoscopy is suggestive of malignancy, but could be misleading in some cases. The aim of the present study was to estimate whether the combination of thoracoscopy with autofluorescence modalities would be useful to further improve the diagnostic accuracy of the conventional method.

The present study displays early results of thoracoscopy performed consecutively with a normal light source and with autofluorescence light in 24 patients with exudative pleural effusion during 2003–2004.

In all cases of malignant pleuritis (carcinoma or mesothelioma), the colour of the affected area of the pleura changed from white/pink to red (sensitivity 100%). However, in two cases of chronic pleuritis, a colour change from white/pink to orange/red was recorded (specificity 75%).

In conclusion, the calculated positive predictive value of colour change for malignant pleuritis during autofluorescence thoracoscopy in this study was 92%. However, the clinical value of autofluorescence thoracoscopy in daily practice remains to be proven.

KEYWORDS: Autofluorescence thoracoscopy, lung cancer, malignant pleural disease, mesothelioma

In 1981, BOUTIN *et al.* [1] reported that in a series of 1,000 consecutive patients with pleural effusions, thoracoscopy was indicated in 215 cases where it established the diagnosis in 97%. The diagnostic yield of medical thoracoscopy in malignant effusions is high: according to LODDENKEMPER and BOUTIN [2] it is 95%, whereas according to BLANC *et al.* [3] it is 93.3% and 90–100% according to COLT [4]. In any case, the sensitivity of thoracoscopy in detecting pleural malignancies is much higher than the sensitivity of percutaneous closed needle pleural biopsy (up to 50% [5]), pleural fluid cytology (from 62–80% when three separate specimens are collected [6, 7]) or even when the two methods are combined (74% [8]). Similar encouraging results have been obtained in studies on the role of thoracoscopy in the staging of patients with bronchial carcinoma or diffuse mesothelioma [2, 9].

The endoscopic appearance of pleural lesions during medical thoracoscopy is suggestive of malignancy in 86% of cases [10]. Suggestive appearances include: nodules, polypoid lesions, masses, malignant thickening of the pleura, and localised ''candle wax drops''. However, there are malignancies which may resemble non-specific inflammation and, conversely, certain inflammatory lesions can mimic tumours. Even mesotheliomas, which usually have a characteristic grape-like nodular appearance, can appear as ordinary inflammation.

To improve the diagnostic accuracy of thoracoscopy, autofluorescence was assessed in combination with the conventional method, as the effectiveness of autofluorescence techniques has been proven in both accurate detection of early malignant or invasive lesions and appropriate sampling of tissue during bronchoscopy. In addition, autofluorescence thoracoscopy (AFT) would be helpful for delineating the tumour margins and, therefore, for precise staging of intrathoracic lesions.

PATIENTS AND METHODS

In total, 24 patients of mean age 66.4 yrs (range 46–82) were prospectively included. Of these, 13 (54%) were male and 11 (46%) were female. All of them had presented with an exudative pleural

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Received:
March 09 2005
Accepted after revision:
July 20 2005

SUPPORT STATEMENT
Both authors do not have a financial relationship with a commercial entity that has an interest in the subject matter of this manuscript. M.G. Chrysanthidis is the recipient of a European Respiratory Society Training fellowship (number SPTF 2003-013) on Thoracoscopy in Canisius Wilhelmina Ziekenhuis – Nijmegen, The Netherlands, 2003.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

effusion and/or abnormal pleural findings on computed tomography scans.

AFT was performed in the endoscopy suite under local anaesthesia. The patients breathed spontaneously and 0.25–0.5 mg atropine and 10 mg morphine was used as the premedication. First, the entire pleural cavity in the examined hemithorax was thoroughly evaluated using conventional thoracoscopy (white light thoracoscopy; WLT), after removing all pleural fluid. The visceral and parietal pleura were inspected with WLT, and areas of abnormal pleura were mapped. The pleural cavity was then inspected with AFT and the change in colour of the areas of abnormal pleura was assessed. Furthermore, the pleural cavity was inspected with AFT for areas of abnormal pleura which were not noticed during WLT inspection. Biopsies of areas of abnormal pleura were subsequently taken for histology analysis. All thoracoscopic procedures under white or blue light were recorded on videotape and reviewed.

THE VIDEOTHORACOSCOPIC AUTOFLUORESCENCE IMAGING DEVICE

The device used in the current study was the Diagnostic Auto-Fluorescence Endoscopy system (DAFE®), recently developed by Richard Wolf GmbH, Knittlingen, Germany. The autofluorescence excitation in the DAFE® system is achieved by means of a 300 W xenon lamp in the violet-blue range (390–460 nm). The photodetection system relies on one charge-coupled device (CCD) camera and a dual detection range (green region of 500–590 nm wavelength and a red region of 600–700 nm wavelength), as at least two spectral domains are necessary for efficient contrast enhancement. A device clipped to the eyepiece of the standard bronchoscope frames the optical elements to: 1) separate the fluorescence light into its colour components; 2) filter unwanted light; and 3) focus the two resulting light beams (one for the green and one for the red region), side by side on the same micro-head CCD camera. The signal is then processed by a delay line, which first duplicates the camera signal and then delays the two resulting signals, thus allowing the superimposition of the two components in false colours on a colour screen. The system is completed with a standard video cassette recorder [11]. In recent studies, the addition of a 3.5 mm spacer, fitted at the distal end of the DAFE® endoscope, ensures that all autofluorescence spectra are taken with the fibre-bundle tip at the same distance from the mucosa surface [12], and that a balance is achieved between two antagonist effects, namely an increase in the probe-sample distance to minimise the geometrical distortion of the spectra and a decrease in this distance to maximise the signal-to-noise ratio [13].

In the process of further development and technical evolution of the DAFE® system, it was recently discovered that the excitation wavelength yielding the highest sensitivity and specificity was >400 nm with a peak value near 405 nm, and that the positive predictive value (PPV) for the tumour detection endoscopies could be raised significantly from 38 to 100% by combining this method with the classical white light endoscopy [12].

With the exception of the imaging device as described before, the AFT system uses the same thoracoscopy equipment as WLT (Wolf thoracoscopy set; 7 mm optical telescope (as developed by C. Boutin); fluid light cables; and Wolf 5 mm biopsy forceps).

RESULTS

Normal areas in the pleural surface appeared white or white/pink in both WLT and AFT in the present study. Areas with fat on the pleural layer appeared yellow under the conventional mode, but orange under the autofluorescence mode.

As shown in table 1, in all cases of histologically proven malignant pleural disease (including nine patients with metastatic pleurae carcinomas and seven cases with mesotheliomas), the colour of the affected area of the pleura changed from white/pink to red in a darker or slighter attenuation (fig. 1). Therefore, the sensitivity of AFT for detecting malignant lesions on the pleural surface was 100%.

However, in two out of eight cases of chronic pleuritis, a colour change from white/pink to orange/red was found. In the remaining six patients there was no difference in pleural surface colour between WLT and AFT. Thus, the specificity of AFT in the present study was 75%.

DISCUSSION

Autofluorescence systems have been widely introduced into clinical practice for the early detection of lung cancer during bronchoscopy [14–16], incorporating the most recent advances of optical technologies to provide accurate imaging. Meanwhile, the fluorescence diagnosis of pleural malignancies has

TABLE 1 Colours of pleural disease during white light thoracoscopy (WLT) and autofluorescence thoracoscopy (AFT)

Biopsy proven diagnosis	WLT	AFT	Patients n
Mesothelioma	White/pink	Red	6
	White/pink	White/red	1
Metastatic pleurae carcinoma	White/pink	Deep red	7
	White/pink	Slighter red	2
Chronic pleuritis	White	White	6
	White/pink	Orange/red	2

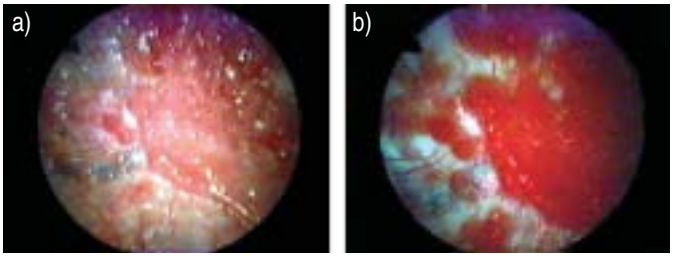

FIGURE 1. Breast cancer metastasis to the parietal pleura as shown by a) white light thoracoscopy (WLT) and b) autofluorescence thoracoscopy (AFT). During WLT the colour of the malignant tissue is light pink. During AFT the malignant tissue is deep red, whereas the normal tissue has turned white. The line between the normal and malignant tissue is well demarcated.

only been attempted in an experimental animal setting [17], as the photosensitiser 5-aminolevulinic acid (ALA) was combined with conventional video assisted thoracic surgery (VATS) to improve tumour staging in advanced lung cancer with pleural tumour spread in rats. Further increase in the diagnostic accuracy of VATS, ~100% sensitivity by precise assessment of disseminated intrathoracic tumour spread, was considered important for determining the resectability of the malignant lesions. PROSST *et al.* [17] induced diffuse pleural carcinosis affecting the entire pleural cavity of nude rats. After 5–7 weeks of tumour growth, a pleural lavage was performed with 1.5 or 3% ALA solution, followed by photosensitisation for 2, 4 or 6 h, after which a conventional white light VATS and a fluorescence examination using the D-Light (Karl Storz, Tuttlingen, Germany)/autofluorescence system were consecutively performed. The same researchers reported that the photosensitiser accumulation in the tumour was up to 11 times higher than in normal tissue and detected up to 30% additional pleural malignant lesions by thoracoscopic fluorescence diagnosis compared with conventional white light VATS alone.

More recently, NOPPEN *et al.* [18] published a case report concerning fluorescein-inhanced autofluorescence thoracoscopy (FEAT) in primary spontaneous pneumothorax. The findings suggest substantial areas of parenchymal abnormality could be found using FEAT, which were undetected by WLT inspection of the parenchymal surface. Furthermore, satellite areas of parenchymal abnormalities could only be identified with FEAT.

Another recent report by BURGERS *et al.* [19], studied 15 patients with suspected pleural malignancies using 5-aminolevulinic acid induced protoporphyrin IX fluorescence. No false positive fluorescence was observed, but 50% of cases had a false negative fluorescence signal.

A limitation of the current study was that biopsies were obtained from a rather restricted number of sites on the pleural space. Therefore, the estimations of the false negatives would not be accurate enough to be taken under consideration in calculating the sensitivity of the method. The ability to find a lesion if there was one (sensitivity) is the most important parameter to characterise the performance of a detection method, but requires the total number of false negatives to be known. It is impossible to have specimens from the entire pleural surface with the object of obtaining an approximately reliable value of false negatives.

The PPV, defined as the probability that a positive result represents a lesion, is thought to be a more realistic parameter for evaluation of AFT as a diagnostic method. In the group of patients who underwent AFT during the present study, the PPV, calculated as the ratio of the true positive results on the overall (true and false) positive results, was 92%.

In the authors' initial experience, AFT is easy to perform, without significant prolongation of the thoracoscopy procedure. In all patients with biopsy proven malignant pleural disease, either malignant mesothelioma or metastatic pleural carcinoma, a colour change from normal white or white/pink to red (in a deeper or slight attenuation) was found. In contrast to a sensitivity of 100% in patients with malignant effusions, two false positive results were found in patients with chronic pleuritis, which resulted in a specificity of 75% in this group.

In conclusion, an important limitation of the current study was that the patients had extended pleural disease at the moment of thoracoscopy, which was easy to diagnose with white light-guided biopsies. The same malignant lesions were easily found and more precisely mapped during autofluorescence thoracoscopy. The findings with blue light were more obvious than with white light, so it is expected that this new technique will be of help in cases without clear malignant appearance during white light thoracoscopy. To prove the additional value of autofluorescence thoracoscopy in clinical practice, a study including cases of malignant pleural disease in an early stage needs to be performed.

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