Sputum cytology in two cases of Wegener's granulomatosis

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SYNOPSIS Two patients with Wegener's granulomatosis are described in whom the sputum was found to contain abnormal cells. The diagnosis was suggested in the second case on cytological grounds alone. It is considered, therefore, that sputum cytology is a relevant investigation in the diagnosis of this condition.

When the nature of the pathological changes in the respiratory tract in Wegener's granulomatosis is considered, namely, necrotizing giant-cell granulomatous areas with focal vasculitis, it is not surprising that abnormal cells can be found in the sputum. One instance of sputum cytology has been reported by Aach and Kissane (1970) in a patient who presented with pyrexia of unknown origin with no pulmonary symptoms, and whose chest x-ray revealed a right upper lobe mass. This, on removal, showed the typical features of Wegener's granulomatosis. Atypical cells were present in the sputum of this patient but they were not described in detail.

Case Reports

CASE 1

Clinical history

In 1972 a 44-year-old housewife was admitted to an ear nose and throat ward with a seven-month history of intermittent bilateral deafness, recurrent sinusitis, and haemorrhagic ulceration of the nasal mucosa. There had also been a non-productive cough for several months. A biopsy of the nasal mucosa showed a granulomatous lesion with inflammatory and giant cells but no marked vasculitis.

While in hospital she became pyrexial (38°C) and the ESR was 90 mm. A chest x-ray showed a right upper lobe opacity which was very suggestive of bronchial carcinoma.

Cytology

Examination of the sputum was performed and the findings are described later. These were regarded

at the time as indicating a probable inflammatory lesion.

In view of the radiological suspicion of malignancy, upper and middle lobectomies were performed. The middle lobe contained an irregular grey mass, 9 cm in diameter, which replaced most of the lung parenchyma.

Histopathology

The mass consisted of a confluent area of granulomatous inflammation with necrosis and with small, separate, miliary foci in adjacent areas. Taken in conjunction with the histological findings in the nasal mucosa, it was considered that, in spite of the relatively slight degree of vasculitis in the latter, the appearances were suggestive of Wegener's granulomatosis.

Large doses of prednisone were administered, but, after initial improvement, the patient died four months after operation.

Necropsy

The disease process was found to be confined to the respiratory tract and showed the typical lesions of Wegener's granulomatosis throughout both lungs.

CASE 2

Clinical history

In 1974 a 28-year-old baker was admitted to a medical thoracic ward with extreme dyspnoea, cough, and haemoptysis following a fall from his motor-cycle one week previously.

At the age of 14 he had had a lobectomy for bronchiectasis of unspecified aetiology. Recurrent episodes of 'bronchitis' occurred over the years until his final illness.

On admission the patient was very ill with a temperature of 38.4°C and an ESR of 45 mm. Proteinuria and haematuria were present. Chest x-rays showed patchy opacities in all zones with cavitation at the left apex, and on this basis a clinical diagnosis of tuberculosis or possible alveolar-cell carcinoma was made.

Cytology

Examination of the sputum was performed and a diagnosis of Wegener's granulomatosis was suggested. The cytological features are described later.

In spite of cytotoxic treatment the patient deteriorated rapidly and died five days after admission.

Necropsy

Macroscopically the characteristic necrotic lesions were found in the lungs and spleen; microscopically they were present also in the kidneys and in skin lesions on the hands, buttocks, and knees previously attributed solely to trauma.

Cytological Features

The sputum samples showed essentially the same features in each case. They contained cellular clusters of varying size, some extremely large and containing several hundred cells (fig 1). Although cilia could not be demonstrated, some of the smaller clumps were bounded by the smooth edge indicative of a brush border (fig 2). The cells of the larger aggregates, while densely packed and overlapping in the centre, were more loosely arranged at the periphery where the features of individual cells could be seen. These cells had pale basophilic cytoplasm which showed little differentiation, although an occasional cell was vacuolated, and a few appeared

Fig 2 Case 1. Small clump of cells with intact brush border (Papanicolaou $\times$ 250).

columnar in shape. The nuclear-cytoplasmic ratio was high, and the nuclei were fairly uniform in size (approx 10-12 μ diam), normochromatic, circular with smooth borders, and, in general, having a relatively open chromatin pattern. The cells at the periphery of the clumps were loosely adherent one to another and, in some cases, lying free. No continuous border was present in any of the larger aggregates, and no cilia were found.

Individual cells were present separately and in small groups, the cytoplasm of which was denser than in the large clumps, with more marked vacuolation and, in some, a hint of concentric lamination. The nuclei of these showed more marked chromatin clumping (figs 3 and 4). Although the cytoplasm of some of these cells presented a somewhat squamoid appearance, these groups were considered to be of bronchiolar origin.

Also present in both cases were large numbers of acute and chronic inflammatory cells, active histiocytes, and red blood cells. The sputum of case 1

Fig 1 Case 2. Large clump of densely packed cells (Papanicolaou $\times$ 325).

Fig 3 Case 2. Group of cells showing nuclear uniformity and one vacuolated cell (Papanicolaou $\times 405$).

Fig 4 Case 1. Group of cells showing clumped chromatin and slight cytoplasmic lamination (Papanicolaou $\times 1250$).

contained numerous multinucleated giant cells, while that of case 2 contained squamous cells showing reactive changes which were considered to originate in the upper respiratory tract.

Special staining failed to reveal mucus-secretory activity, and it was thought that the vacuolation was a degenerative feature.

Discussion

The small, smooth-edged clumps (fig 2) were easily identifiable as being of bronchial epithelial origin, benign in nature, and similar to those commonly found in asthma and other conditions featuring benign bronchial epithelial proliferation. The large aggregates were more difficult to assess, presenting, as they did, one of the problems familiar to the cytologist, namely, the differential diagnosis between benign hyperplastic and adenocarcinomatous cells (in this case of bronchiolar type). Because of the absence of conclusively malignant features, it was considered that the appearances indicated some extremely hyperplastic condition of the bronchiolar epithelium rather than a malignant one. At the time when case 1 was under consideration and before the diagnosis was known, it was observed that the clusters of bronchiolar cells were unusually large in size for a benign condition, consisting, as

some did, of several hundred cells. Indeed, when the sputum of case 2 was examined two years later, it was largely on the basis of similar cell clusters that the diagnosis was suggested.

A bronchiole from case 1 is shown in figs 5 and 6, where the hyperplastic epithelium appears to be in the process of being exfoliated, and there is little doubt that the cytological findings reflect the extensive shedding of this epithelium. The unusual cytological feature in the two cases concerned, namely, the *size* of the clumps, is a matter of quantity rather than quality and may therefore be an indication merely of the extent of the pathological process rather than of any inherent abnormal property of the cells themselves. It is possible, indeed, that any inflammatory lesion involving the bronchioles to this degree would exfoliate similar clumps. However, in a considerable experience of sputum cytology, I have not seen this picture in any comparable pathological lesion, such as pneumonia, bronchitis, and tuberculosis.

In these two cases there was already marked clinical evidence of lung involvement when the sputum was examined, and it is possible that it is only at this advanced stage that abnormal cytological features are evident. It is worth noting that one patient had a history of 'cough' for several months, while the other had suffered from 'recurrent bron-

Fig 5 Case 1. Bronchiole from resected lobe showing epithelial proliferation (H and E $\times 105$).

Fig 6 Case 1. Higher power view of bronchiole showing area of detached epithelium (H and E $\times 255$).

chitis', both histories suggesting a long-standing bronchial involvement. It would be interesting to know at what stage in the disease abnormal cells appear in the sputum, and whether, as in the case of lung tumours, cytological examination can reveal abnormal findings before clinical or radiological evidence is available. At present, clinical diagnosis is frequently delayed or even retrospective, due partly to the often insidious onset of the disease and partly to reliance on a single biopsy which may, in itself, be inconclusive. If it transpires that an abnormal cytological picture is to be found early in the disease, the examination of the sputum of patients with chronic upper respiratory complaints, particularly when associated with haemorrhagic ulceration, should be a useful investigation in making an early diagnosis. Whether or not this is the case, it has been established from the experience of these two cases that, when hyperplastic bronchiolar cell clusters are found in the sputum, the possibility

of Wegener's granulomatosis should be borne in mind in the differential diagnosis. In view of the improved prognosis of this condition with cytotoxic therapy (Fauci *et al*, 1971; Patchefsky and Israel, 1973), its early diagnosis has become increasingly important.

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