Immunohistochemistry for small cell carcinoma a potential diagnostic pitfall

Immunohistochemistry for small cell carcinoma: a potential diagnostic pitfall.

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The morphological appearances of small cell lung carcinoma (SCLC) are often characteristic however immunohistochemistry (IHC) is frequently employed to support the diagnosis, especially when there is crush artefact (1). In general histopathologists look for expression of cytokeratins, CD56 and TTF1 but it is well recognised that SCLC may not show typical staining reactions. While CD56 is usually expressed TTF1 may be negative and cytokeratin staining may be very focal or even absent (1,2). We report three cases of mediastinal alveolar rhabdomyosarcoma who presented with radiological features of lung cancer where the morphological and immunohistochemical profile mimicked SCLC.

Case 1

An 81 year old male presented with an extensive paratracheal nodal mass and a clinical/radiological diagnosis of lung cancer. An endobronchial ultrasound fine needle aspiration revealed necrotic debris admixed with a population of malignant cells (Fig 1). The cells were of intermediate size with limited cytoplasm and finely granular chromatin. Immunohistochemistry showed tumour cell expression of cytokeratin AE1/3 and CAM5.2 with a paranuclear ‘dot’ pattern, CD56 and focally nuclear staining for TTF1. Staining for synaptophysin was negative. The initial impression was that this was a high grade carcinoma with neuroendocrine features and a diagnosis of SCLC was considered. Further immunohistochemistry, however, showed the cells to express desmin, myogenin and MyoD1 and a diagnosis of rhabdomyosarcoma was made.

Case 2

A 70 year old female presented with enlarged mediastinal lymph nodes and a tumour invading the left pulmonary artery. A CT guided biopsy showed a tumour comprising epithelioid cells with minimal cytoplasm, finely granular hyperchromatic nuclei and inconspicuous nucleoli with evidence of moulding (Figure 2). The morphological features were suggestive of SCLC. Immunohistochemistry showed no convincing staining with

cytokeratin AE1/3 or CK7 but there was expression of CD56 and synaptophysin with some very focal expression of TTF1. Further IHC showed the tumour cells to express desmin, myogenin and MyoD1 and a diagnosis of rhabdomyosarcoma was made.

Retrospective audit and case 3

A review of the pathology archive within the Royal Infirmary of Edinburgh revealed 156 cases diagnosed as small cell carcinoma in 2016 (n=73) and 2017 (n=83). 28 (18%) had been diagnosed on morphology alone (3 had no material for IHC). 108 (68%) showed typical expression of cytokeratin, CD56 and TTF1. 14 were cytokeratin positive, CD56 positive but TTF1 negative; 1 was CD56 positive, cytokeratin and TTF1 negative; 1 was cytokeratin positive, CD56 and TTF1 negative and 3 were cytokeratin and TTF1 positive, CD56 negative.

IHC staining for desmin was carried out on the 19 cases which had not shown typical positive staining. One case was identified as expressing desmin and was subsequently shown to also express myogenin and MyoD1. This biopsy was from a 71 year old male patient with a right mediastinal / supraclavicular fossa mass. The tumour comprised islands of cells forming cohesive sheets with focal necrosis. The cells had scanty cytoplasm and nuclei with finely granular chromatin and inconspicuous nucleoli. IHC had shown expression of CD56 but no convincing expression of cytokeratin CAM5.2 or TTF1.

Discussion

The literature on the differential diagnosis of SCLC and the use of IHC has concentrated on distinguishing these tumours from carcinoids, other non-small cell carcinomas and lymphoma (2,3). Bahrami et al (4) has, however, previously highlighted that the IHC routinely used to characterise SCLC is frequently expressed by alveolar rhadomyosarcomas. In their study of 44 alveolar rhabdomyosarcomas (age range: <1-64 years) 50% expressed wide

spectrum cytokeratins and CD56 expression was described as ubiquitous. In addition 32% expressed synaptophysin and 22% expressed chromogranin. Concurrent expression of epithelial and neuroendocrine markers was observed in 30-40% of their cases and they commented that the morphology and the high frequency of expression of both cytokeratins and neuroendocrine markers posed a risk, especially in adult patients, of misdiagnosis as small cell carcinoma and other neuroepithelial tumours.

Interestingly in two of our cases the tumour showed focal but definite nuclear expression of TTF1 (Dako 8G7G3/1). Idiosyncratic TTF1 expression has previously been reported at low frequency in a range of carcinomas from different sites although the frequency of this may be related to the clone of antibody used (5). Expression by soft tissue tumours, however, appears even more unusual although there is one report of expression by seven of eight nephroblastomas (6). To our knowledge no previous description of TTF1 staining in rhabdomyosarcomas has been reported.

In conclusion, these cases indicate that even when the clinical/radiological and morphological features are suggestive of SCLC but IHC shows incomplete, or only very focal, expression of a triad of immunostains for cytokeratins, CD56 and TTF1 the possibility of a ‘small blue round cell tumour’ other than small cell carcinoma needs to be considered. Our experience suggests that alveolar rhabdomyosarcoma would appear to present a particular risk for mis-diagnosis in this setting given its frequent expression of cytokeratins and markers of neuroendocrine differentiation.

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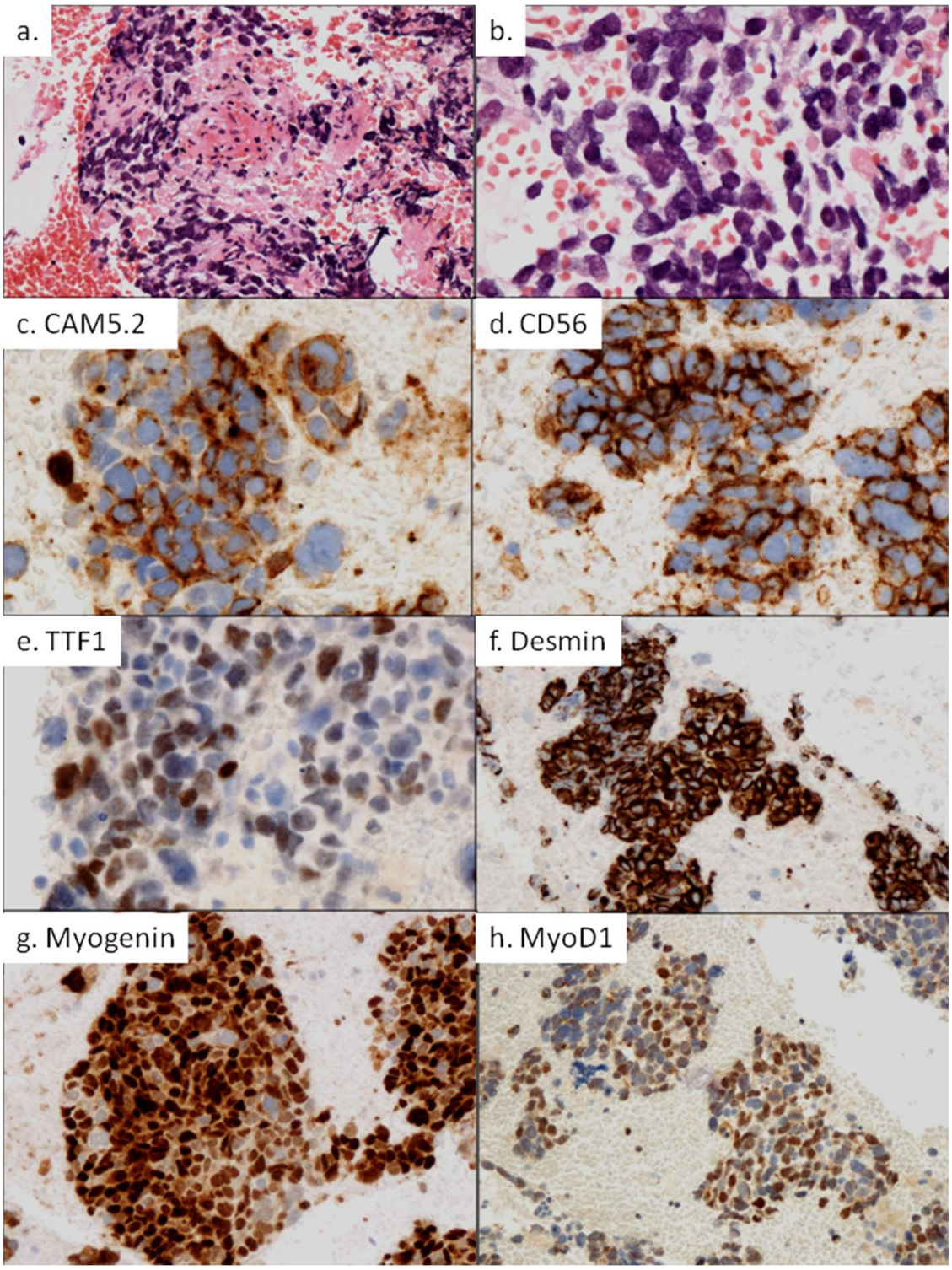

Figure 1

Case 1. Photomicrographs of the tumour cells identified in the cell block produced from an EBUS – FNA of the mediastinal mass. The specimen comprises groups and sheets of malignant cells with scant cytoplasm, predominantly oval nuclei and inconspicuous nucleoli. Immunohistochemistry shows expression of the cytokeratin CAM5.2 with a focal paranuclear dot pattern as well as CD56 and, focally, TTF1. The tumour cells also show expression of desmin, myogenin and MyoD1. (A H&E x200; B H&E x400; C-E IHC x 400; F-H IHC x 200).

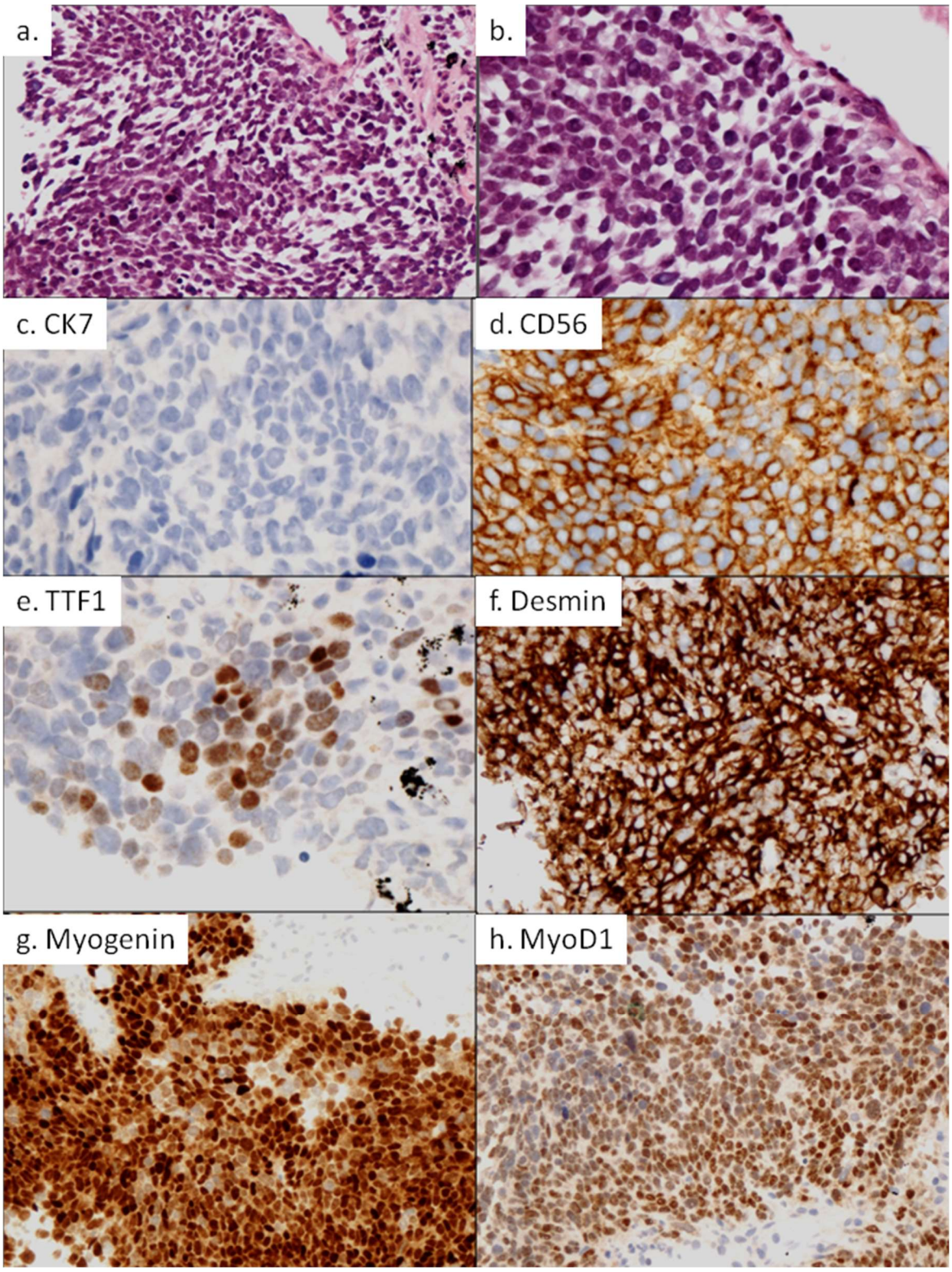

Figure 2

Case 2. Photomicrographs of the tumour in the CT core biopsy obtained from the mediastinal mass. The biopsy shows infiltration by a malignant tumour which predominantly is composed of cell with scant cytoplasm, oval nuclei and granular chromatin. Nucleoli were indistinct. Immunohistochemistry demonstrates expression of CD56 and focally TTF1 but not cytokeratins. The tumour cells also show expression of desmin, myogenin and MyoD1. (A H&E x200; B H&E x400; C-E IHC x 400; F-H IHC x 200).