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Papers

Malignant Cells of Epithelial Phenotype Limited to Thoracic Lymph Nodes

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Asymptomatic thoracic lymphadenopathy was incidentally discovered in three patients with no definitive diagnoses. Enlarged lymph nodes, removed at thoracotomy, had irregularly distributed, pleomorphic, malignant-appearing cells. Mitoses were frequent. Electron microscopy showed tonofilament bundles and desmosomes. By immunocytochemistry, these cells uniformly expressed desmoplakin and cytokeratins 8 and 18 and various patterns of coexpression with other cytokeratins. One patient had lymphadenectomy, segmental lung resection and radiotherapy; the second had lymphadenectomy and later a lymphadenectomy with pneumonectomy; and the third had lymphadenectomy and radiotherapy. Neoplastic cells were detected exclusively within thoracic lymph nodes. The patients are well 111, 39 and 13 months after initial presentation. The clinical course and the patterns of intranodal distribution and marker expression of the neoplastic cells are unusual and distinct from most carcinomas metastatic to lymph nodes and reminiscent of "lymphoepithelioma-like carcinomas" described in the thymus and other sites. While the malignant cells may reflect metastases from as yet occult primaries or malignantly transformed ectopic epithelial nests, these tumours may arise by transformation from the cytokeratin-positive "extrafollicular reticulum cells" indigenous to lymphoid organs.
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INTRODUCTION

THE DEVELOPMENT of metastases in lymph nodes is a characteristic feature of the natural history of most epithelial malignancies. Depending on the tumour stage at initial diagnosis, lymph node metastases are detected in situations of known primary carcinomas or may develop and/or be detected subsequently. In a minority of cases, visceral carcinomas are discovered by detection of lymph node metastases [1, 2]. Lymphoepitheliomas (or poorly differentiated carcinomas) of the nasopharynx (LEN) are exceptional in that most cases are first diagnosed by the finding of tumour cells in cervical lymph nodes [3, 4]. During the past decade, tumours histologically similar to LEN and termed lymphoepithelioma-like carcinomas (LLC) have been described in the thymus [5–7], salivary glands [8, 9], uterine cervix [10], skin [11] and lung [12]. What is notable about many cases of LEN and some LLC cases is their association with Epstein–Barr virus (EBV) [13–15].

We report patients who presented with asymptomatic thoracopulmonary lymphadenopathy; extensive examination failed to show primary carcinomas. Lymph node biopsies revealed individual or clustered malignant epithelial cells intimately associated with lymphoid elements. The clinico-pathological findings and the unusual patterns of differentiation marker proteins suggest that these malignant cells may have originated in the lymph nodes.

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PATIENTS AND METHODS

Patients

Case 1 (57-year-old Caucasian man, 2 week history of coughing dark clotted blood). He smoked one pack of cigarettes daily. He had a history of wheezing and was being treated with bronchodilators and theophylline. Physical examination was unremarkable. There was no cyanosis or clubbing; examination of the head and neck was normal without evidence of lymphadenopathy. Rhonchi were heard over the left base but air entry was otherwise normal. The admission chest radiograph showed a subtle left hilar enlargement confirmed by tomography. The thymic region was normal. Bronchoscopy revealed an endobronchial polypoid nodule in the superior segment of the left lower lobe. Bronchial biopsy specimens showed chronic inflammation. A left thoracotomy revealed several enlarged, firm lymph nodes around the left lower lobe bronchus. A frozen section of a lymph node was diagnosed as "squamous carcinoma" ; the superior pulmonary segment was resected. Extensive sampling of the lung disclosed no tumour; the 4 mm endobronchial polyp consisted of fibrous tissue and some vessels and the mucosa was normal. 6 out of 8 permanent lobar lymph node sections were diagnosed as "metastatic carcinoma" since no keratinisation (as traditionally defined) was noted. Several mediastinal nodes were free of tumour. The patient was subsequently treated with 50 Gy external beam radiotherapy. He is well and free of disease over 9 years later. Immediate postoperat-

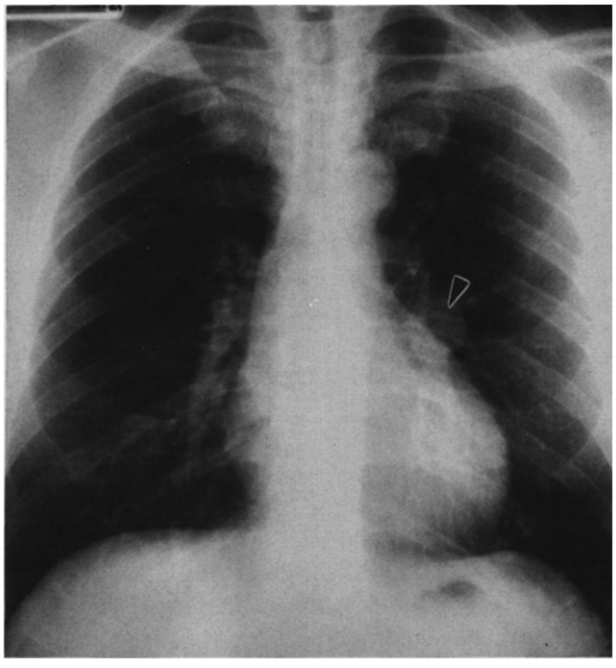

Fig. 1. Chest radiograph (case 2) demonstrating a smooth-walled, well circumscribed left hilar nodule (arrow).

ive and recent studies for EBV revealed the following (stable) antibody titres: early antigen 32, capsid antigen IgG 512 or more and IgM less than 20, and nuclear antigen 80 or more.

Case 2 (44-year-old black man, 4 month history of intermittent blood streaked sputum). He smoked one pack of cigarettes daily for 30 years. He was hypertensive on no medication. Physical examination was unremarkable. A chest radiograph showed a "smooth walled" nodule at the left hilum (Fig. 1). Three bronchoscopies were done; no mucosal lesion was found. Computed tomography (CT) of the chest showed the nodule to be outside the left main stem bronchus; no lung or thymic lesion was noted. CT-directed needle biopsy yielded no diagnostic tissue. A left thoracotomy was done; the anterior mediastinum was normal and no lung lesion was found. A firm, 4 cm lymph node was resected from the aortopulmonary window. Frozen section diagnosis was "malignant cells of undetermined type"; permanent section diagnosis was "poorly differentiated carcinoma". No additional therapy was given. 20 months later, he developed a second left hilar mass confirmed by CT to be immediately medial to the previous; the thymic region remained normal. A nuclear bone scan and CT of the brain were negative. A second thoracotomy was done. Samples of lymph nodes again showed malignant cells, whereupon a left pneumonectomy was done although no parenchymal lesion was noted. Extensive gross and microscopic study of the lung specimen revealed no significant abnormality. The patient is alive and well over 3

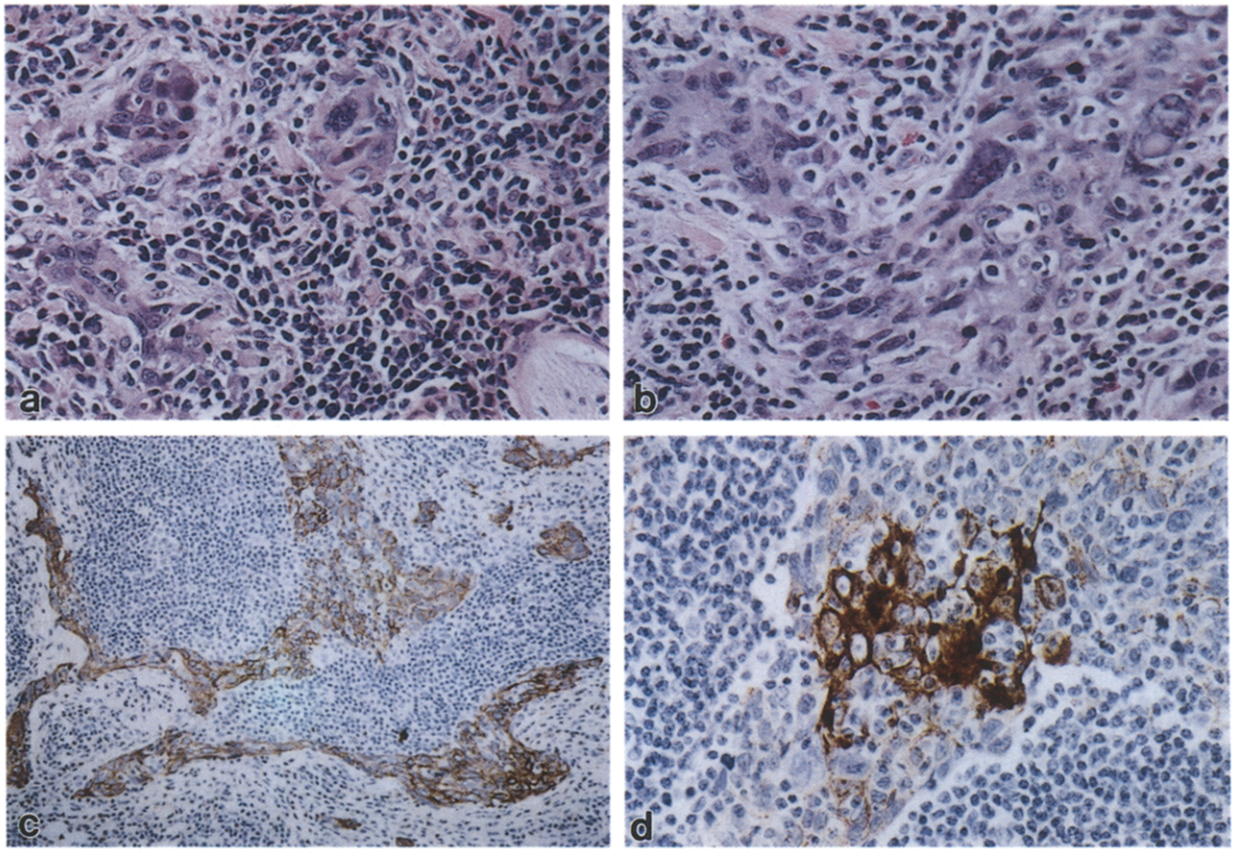

Fig. 2. a = photomicrograph of case 1 depicting small clusters of malignant cells intimately admixed with lymphoid elements, haematoxylin/eosin, × 420. b = case 2, high magnification of perifollicular cord of malignant cells, haematoxylin/eosin, × 640. c = case 2, low magnification immunostain with AE1 cytokeratin antibody outlining cords of positive cells surrounding lymphoid follicle, ABC technique × 170. d = case 1, high magnification immunostain with AE3 cytokeratin antibody showing strong reactivity in small tumur cell cluster, ABC technique × 420.

years after presentation. Recent determinations of EBV antibody titres were: early antigen 32, capsid antigen IgG 512 or more and IgM less than 20, and nuclear antigen 80 or more.

Case 3 (61-year-old non-insulin dependent diabetic man; presented with impaired vision and was undergoing preoperative testing for cataract surgery). A chest radiograph revealed an asymptomatic right hilar mass. He was said to smoke two packs of cigarettes daily. Examination of the head and neck was unremarkable; no adenopathy was noted. Cardiovascular and chest examinations were also normal. CT of the chest revealed the mass to be in the right paratracheal region but extending anterior to the right mainstem bronchus and into the subcarinal space. No thymic or intrapulmonary tumour was detected. Bronchoscopy disclosed no significant abnormality. Mediastinoscopy was done; biopsy samples of firm, enlarged lymph nodes in the right paratracheal region were diagnosed as "poorly differentiated malignant tumour". A right thoracotomy was done with resection of the mediastinal mass. Since the diagnosis of lymphoma was considered and no pulmonary lesions could be demonstrated, no lung was resected. Upon establishing the diagnosis of "carcinoma in lymph nodes", the patient received 50 Gy external beam radiotherapy. He is well 13 months after initial presentation. Recent determinations of EBV antibody titres were: early antigen 32, capsid antigen IgG 512 or more and IgM less than 20 and nuclear antigen 80 or more.

Histological, electron microscopic and immunohistochemical studies

Lymph node and lung samples were fixed for light microscopy in 10% formalin or Bouin's solution and for electron microscopy in 2.5% glutaraldehyde, and processed conventionally. Fresh samples in two cases were snap-frozen in liquid nitrogen and stored at −80°C. Paraffin sections were stained with haematoxylin/eosin. Further sections were immunostained by the avidin-biotin-complex (ABC) method with antibodies to various cytokeratins (CKs), vimentin, chromogranin A, neurone specific enolase (NSE), synaptophysin, adrenocorticotropic hormone, bombesin, calcitonin, L-enkephalin, somatostatin, serotonin, S-100 protein, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), factor VIII-like antigen and leucocyte common antigen (LCA). Cryosections were studied by immunofluorescence microscopy with antibodies to all classes of intermediate filament proteins, desmoplakins, desmoglein and involucrin, both as single and as double label stainings. Sources and characterisation of antibodies and antisera, and details of methods have been described [16, 17].

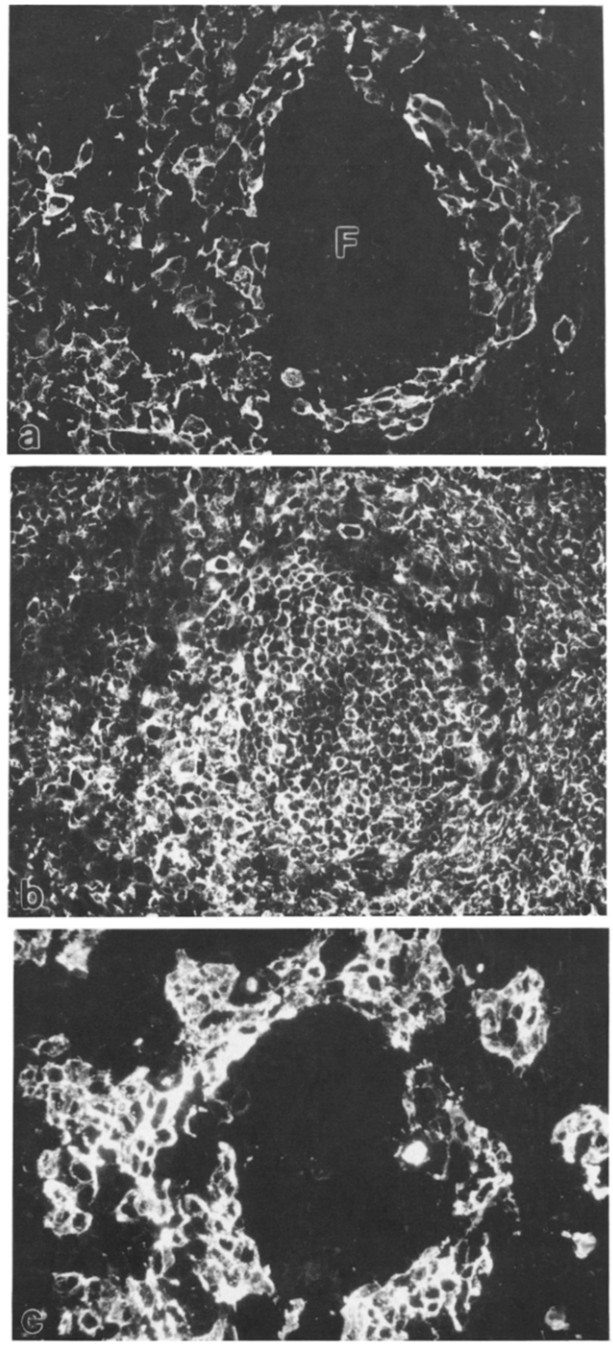

Fig. 3. Case 2, double-label immunofluorescence microscopy with polyclonal antibody to cytokeratins 8 and 18 (a) and monoclonal antibody to vimentin (b). Note extensive and strong reaction in large pleomorphic cells surrounding negative lymphoid follicle (F) in (a). Extensive vimentin reaction is seen in (b) in lymphoid follicle cells while many but not all cytokeratin-positive cells are also vimentin positive, × 175. Double-label immunofluorescence with polyclonal antibody recognizing cytokeratins 8 and 18 that stained virtually all epithelial cells (not shown); panel (c) is stained with monoclonal antibody IC7 recognizing cytokeratin 13 showing that virtually all epithelial cells are strongly reactive, × 230.

RESULTS

In lymph node samples from all three cases, there were highly atypical, pleomorphic non-lymphoid cells with large nuclei and prominent nucleoli. Mitoses were frequent. In cases 1 and 2, the cells were large, with abundant eosinophilic cytoplasm and organised in irregular nests and cords, often closely packed (Figs 2 and 3). A circumferential arrangement around lymph follicles was conspicuous in case 2. In case 3, the cells were smaller and were arranged more loosely, sometimes individually or in cords intimately admixed with lymphocytes; their cytoplasm was pale and ill-defined (Fig. 4).

Immunohistochemical findings are outlined in Table 1. In all three cases, the atypical cells stained uniformly and strongly with antibodies reactive with CKs 8 and 18 (Figs 3a and 4) as well as with desmoplakin and desmoglein antibodies; the latter two showed the typical punctate pattern along cell-to-cell borders (not shown). In two cases, considerable, albeit variable, subpopulations stained with several antibodies to individual CK polypeptides, including some that are commonly considered characteristic of stratified epithelia, such as 13 (Fig. 3c) and 14; however, only variably sparse cells were positive with antibodies to CKs 10 or 11, and 17 (not shown). In contrast, in case 3, only

antibodies reactive with CKs 8 and 18 were strongly and uniformly positive. In all cases, a large cell subpopulation showed co-expression of vimentin with cytokeratin (Fig. 3a, b). In case 2, occasional cells reacting with desmin antibodies and antibodies to smooth muscle alpha-actin were seen in coexpression with CKs (not shown). Immunoreactions with antibodies to CKs 1–4 and 7, to other intermediate filament proteins, to involucrin, LCA, factor VIII-like antigen, S-100 protein, synaptophysin, several neuropeptides and serotonin were negative. Rare cells in case 1 reacted with antibodies to chromogranin A and an antiserum to NSE.

By electron microscopy, the neoplastic cells in all cases displayed numerous and prominent tonofilament bundles, many of which converged towards well developed desmosomes (Figs 5a, b); neither lumina nor microvilli were seen.

To date, in all three patients, no additional lymphadenopathy or any tumour have been found.

DISCUSSION

Abundant and, by conventional criteria, malignant epithelial cells were found in multiple, clinically asymptomatic but enlarged thoracic lymph nodes from three patients in whom no visceral or any other primary tumour was identified, either initially or after follow-up ranging from 13 months to over 9 years. This raises the question whether the malignant cells found in the lymph nodes represent metastatic carcinoma or might have endogenously arisen in the interfollicular region of the lymph nodes themselves.

The malignant cells displayed prominent epithelial characteristics, including CK tonofilaments and numerous desmosomes, leaving no doubt as to their epithelial differentiation. Their pattern of expression of CKs and other cytoskeletal proteins, however, was very unusual in two of the cases (1 and 2) in that many of the cells produced, in addition to the "simple epithelial" type CKs 8 and 18, several other CKs, including the type I CKs 13 and 14 typical of many stratified epithelia, but not necessarily the corresponding type II CK [18, 19]; in particular, CK 4 was missing. The cells were also devoid of involucrin, another protein common to many stratified epithelia and to typical squamous carcinomas [20], including those arising in the nasopharynx [21]. On the other hand, the cells rather frequently co-expressed vimentin and, in one case and very sparsely, also desmin, both intermediate filament proteins rarely occurring in squamous cell carcinomas [22, 23]. The malignant cells also differed in their cytoskeletal marker pattern from the indigenous interfollicular reticulum cells which form intermediate filaments containing CKs 8 and 18 but lack desmosomes and the other CKs [24, 25], but were somewhat reminiscent of the thymic epithelial reticulum and of certain variants of thymomas [18, 26].

Table 1. Immunohistochemical profile of malignant epithelial cells in thoracic lymph nodes

	Case 1*	Case 2†		Case 3†
		Jan 1988	Oct 1989	
Monoclonal antibodies				
CK 1	ND	–	—	—
CK 3	ND	–	—	—
CK 4	ND	–	—	—
CK 5	ND	1+	1+	—
CK 7	ND	—	—	—
CK 8	2+	3+	3+	3+
CK 10	ND	—	—	—
CK 10 and 11	—	1+	1+	—
CK 13	1+	2+	2+	—
CK 14	ND	2+	2+	—
CK 17	ND	1–2+	1–2+	—
CK 18	2+	3+	3+	3+
CK 19	2+	3+	3+	—
CK pan-(lu5, 8. 132)	3+	3+	3+	3+
AE1	3+	3+	3+	3+
AE3	2+	3+	3+	3+
Vimentin	2+	2+	2+	2+
NF-L	—	—	—	—
NF-M	—	—	—	—
NF-H	—	—	—	—
GFP	—	—	—	—
Desmin	—	1+	1+	1+
Desmoplakins 1 and 2	2+	3+	3+	3+
Desmoglein	2+	3+	3+	1–2+
α-smooth muscle actin	1+	1+	1+	1+
Involucrin	—	—	—	—
Chromogranin A	1+	—	—	—
Synaptophysin	—	—	—	—
EMA	1+	1+	1+	—
CEA	1+	1+	1+	—
LCA	—	—	—	—
Factor VIII-like antigen	—	—	—	—
S-100	—	—	—	—
Antisera				
NSE	1+	—	—	—
Serotonin	—	—	—	—
ACTH	—	—	—	—
Bombesin	—	—	—	—
Calcitonin	—	—	—	—
L-enkephalin	—	—	—	—
Somatostatin	—	—	—	—

*Only paraffin sections available. † snap-frozen and paraffin sections available. ND = not done. – = negative, 1+ = rare positive cells, 2+ = many but not all cells positive and 3+ = virtually all cells positive. NF-L, NF-M and NF-H = neurofilament proteins of low, medium and high molecular weight, respectively and GFP = glial filament protein.

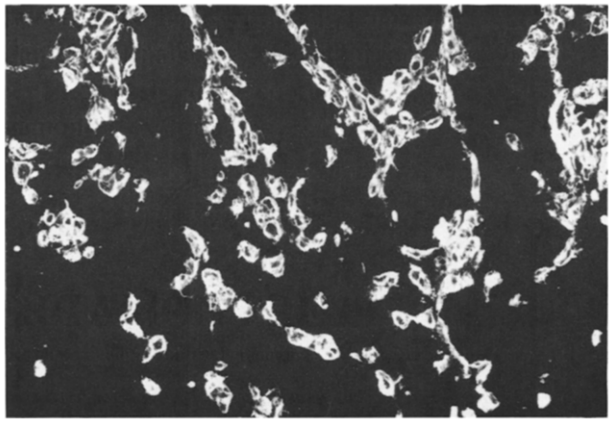

Fig. 4. Case 3, single-label immunofluorescence. Neoplastic cells arranged singly or in small groups are strongly reactive with a monoclonal antibody recognising cytokeratin 18, × 230.

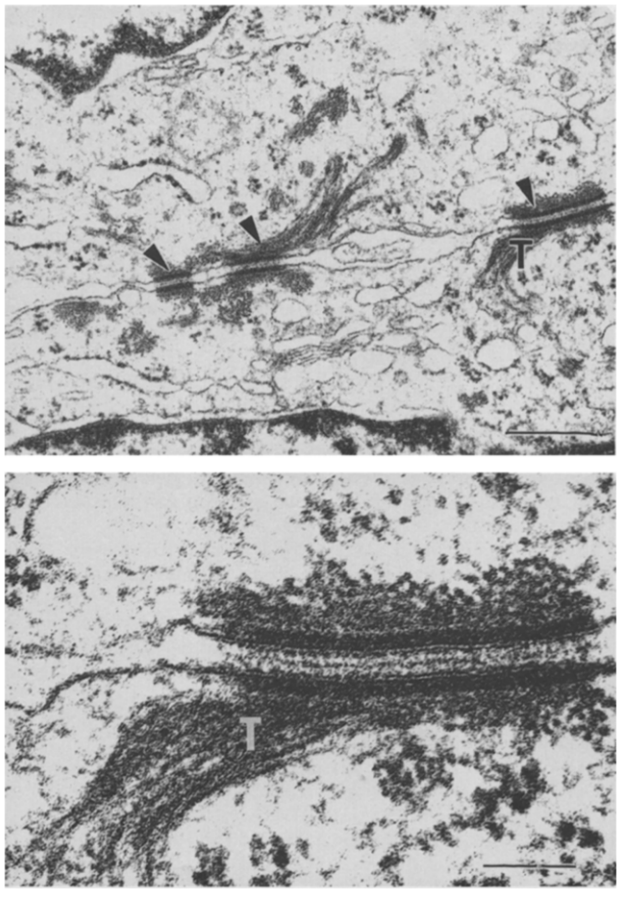

Fig. 5. Case 2, a = electron micrograph showing portions of two adjacent neoplastic epithelial cells. Note prominent tonofilament bundles (T) and frequent desmosomes (arrow heads), × 32 400, bar = 0.5 μm. b = high magnification of desmosome depicting converging filaments (T) and details of junction, × 124 000, bar = 0.1 μm.

Our cases had remarkable clinico-pathological similarities with typical LEN. The lack of symptoms at discovery, the peculiar distribution of the malignant cells in the lymph nodes and their intimate intermingling with lymphoreticular elements, and the non-identification of a synchronous (or metachronous) primary carcinoma are strongly reminiscent of LEN. Also, LENs are less aggressive than conventional nasopharyngeal squamous carcinomas and respond favourably to radiotherapy, thus again paralleling findings in our cases. Clinically, LENs rarely present or become fungating or ulcerated tumours, even in very advanced cases [27–29]. Multiple "blind" biopsies of the nasopharynx may eventually yield tumour cells; yet these samples are as a rule small and distorted to the point that, whereas the presence of malignant cells may indeed be proven, their relation to the overlying mucosal epithelium remains unclear. Indeed, the mucosa often tends to appear intact suggesting that LEN may originate from the submucosa [30]. These apparent paradoxes were noted since LENs were defined as a clinico-pathological entity. Shortly thereafter, in 1929, Ewing [31] entertained the idea that LEN "seems to spring directly from the lymphoid reticulum", and added that "some tumours of the thymus present the most characteristic features" of LEN. At that time, the participation of epithelial cells in the formation of the thymic reticulum was an accepted notion, and Ewing felt it was obscure that such a feature should be restricted to the thymus among lymphoid organs.

For several decades, the possibility that essentially epithelial neoplasms could arise in lymphoid organs other than the thymus was virtually but not entirely abandoned. Astute observers, such as von Albertini and Roulet [32], suggested that LEN were "tissue specific" tumours arising in what they termed lymphoepithelial organs. It was further speculated that LEN could arise from thymic epithelial rests in Waldeyer's ring [33] and this thought was reinforced by the description of thymic remnants in the posterior pharynx [34]. Yet these notions could not be solidly built upon given the prevailing concept that lymph nodes possessed no specific lymphoepithelium from which LEN could arise [3].

In 1987, an extensive "extrafollicular reticulum" of cells with epithelial features such as constitutive intermediate filaments containing CKs 8 and 18, but without desmosomes, was described in lymphoid organs, including nodes, tonsils and spleen [24, 25]. Subpopulations of these reticulum cells variably coexpressed CK intermediate filaments with vimentin, desmin and smooth muscle alpha-actin [24]. These distinct reticular elements indigenous to lymphoid organs thus represent a cell population from which neoplasms with epithelial features may indeed arise, including types in which further epithelial differentiation markers may be acquired, such as the formation of desmosomes and the synthesis of additional CKs. Notably, the cytoskeletal profile demonstrated in our cases has similarities with features of the epithelial reticulum of the thymus; parallels include the high complexity of CK expression in mosaic patterns [18, 26], the frequent coexpression of CKs with other intermediate filament [26], the presence of typical desmosomes, and even the occasional occurrence of neuroendocrine differentiation markers.

An alternative notion that may explain the presence of these malignant epithelial cells in thoracic lymph nodes is that they represent metastases from as yet occult primary carcinomas. While this explanation cannot be totally excluded, it seems unlikely given the times already elapsed, the presence of tumour cells in multiple lymph nodes but not in other sites (including the case that developed "recurrences") and certain striking clinical, morphological and therapeutic similarities between these cases and classical LEN [8, 12, 27–29].

Lastly, we may consider that the tumour cells in these lymph nodes may have resulted from the transformation of "ectopic" epithelial nests, which have been noted in cervical lymph nodes where they resemble thyroid follicles [35] or salivary gland ducts [36], in pelvic and retroperitoneal lymph nodes, where they may mimic mullerian epithelium [37, 38], and in axillary lymph nodes, where they may imitate breast ducts [39–40]. While these structures are well known to most pathologists, neoplasms presumably arising from them are exceedingly rare [41, 42]. To our knowledge, similar structures have not been described in thoracopulmonary lymph nodes although their existence cannot be ruled out.

Classical LENs display all criteria of malignancy, including the capability to establish distant metastases in, for instance, liver and bone [8, 9]. While metastatic capability is yet to be displayed by our cases, the similarities with LEN would suggest that they may represent primary LLCs in lymph nodes. Alternatively, we may speculate on the existence of a lower grade, multifocal, proliferative process of epithelium-like reticulum cells of lymphoid organs capable of recurrences which could be tentatively designated as "epithelial reticulosis".

The possibility that the described malignant cells in lymph nodes may have arisen from indigenous extrafollicular reticulum

cells merits serious consideration. If this concept were substantiated, one might argue that at least some instances of classical LEN may similarly arise from cervical lymph nodes or from pharyngeal submucosal lymphoepithelial aggregates, as suggested by von Albertini and Roulet [32]. Furthermore, given the finding of such neoplastic populations in lymph nodes of the thorax, and possibly other chains, but in the absence of a detectable primary carcinoma, caution would appear warranted before the final diagnosis of metastatic carcinoma is issued and before undertaking extensive surgery or aggressive chemotherapy. We also expect that lymph node neoplasms of the type described here have puzzled other pathologists as well.

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