CASE REPORT

Clear cell “sugar” tumour of the lung: a case report

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Abstract

We report a case of clear cell “sugar” tumour of the lung (CCTL) occurring in a 26-year-old lady. The patient was asymptomatic and the lesion was picked up in the course of a pre-employment medical examination. A well-defined 5 cm nodule in the right lower lobe was detected on routine chest X-Ray. Microscopical examination of the coin lesion showed clear cells containing abundant diastase-sensitive intracytoplasmic glycogen, as demonstrated with periodic acid-Schiff stains. Tumour immunoreactivity for HMB-45 and non-reactivity for cytokeratin support the histological diagnosis. To our knowledge, this is the first reported case of CCTL in Malaysia.

Key words: Lung, pulmonary, asymptomatic, chest x-ray, clear cell, glycogen, HMB-45

INTRODUCTION

Clear cell tumours of the lung (CCTL) are rare pulmonary neoplasms of uncertain histogenesis first described by Liebow and Castleman in 1963.1,2 Although a number of cases have since been published in the literature, it remains an extremely rare primary pulmonary tumour. The differentiation of this tumour has been enigmatic and controversial. Evidence for several different lines of differentiation have been reported, including neuroendocrine,3 myogenic or pericytic,4 epithelial,5 and melanocytic.6 More recent studies have reported the presence of intracytoplasmic premelanosomes, membrane-bound electron-dense granules, and immunohistochemical staining for HMB-45 in the tumours.6-9

CASE REPORT

Clinical findings

CNP, a 26-year-old lady, in the course of a routine medical check-up as part of requirement for employment, was discovered to have a nodular shadow in the lower zone of her right lung (Figure 1). She was otherwise asymptomatic, was married and had one child. She is a non-smoker.

CT chest scan confirmed a 3.7 x 3.7 x 5.2 cm nodule in her right lower lobe. There was no mediastinal lymphadenopathy. The brain and abdomen CT scans ruled out spread to the brain, liver and supra-renal glands.

The patient underwent bronchoscopy, which was essentially normal. She was subjected to right thoracotomy and a lower lobectomy was performed. Her recovery was uneventful and she was discharged a week later.

Pathological Examination

On gross examination, the tumour measured about 5 cm in its largest dimension, was well-circumscribed, and had a homogenous creamy white appearance on inspection (Figure 2).

Light microscopical examination showed a proliferation of round and oval cells with typical round nuclei, indistinct nucleoli and abundant clear cytoplasm (Figure 3). The stromal vascularity was prominent, with vascular channels coursing through the tumour cells. There was no necrosis, haemorrhage, mitoses or cytological atypia of the tumour cells.

The PAS staining reaction revealed abundant glycogen granules in the cellular cytoplasm, and these were removed by diastase pre-treatment before staining. Immunohistological examination revealed that all cells were uniformly and strongly positive for HMB-45 (Figure 4). There was weak focal staining with neurone specific enolase,
and the cells were negative for S-100 protein. The cells were also negative for CD34, and the antibody served to delineate the vascular stroma clearly.

**DISCUSSION**

Since Liebow and Castleman’s original report in 1963, more than 40 cases of CCTL and a single case of clear cell tumour of the trachea have been published.\(^8,10\) There is a slight female preponderance among the patients, who range from 8 to 67 years of age (median 57 years). Tumours are most often peripheral coin lesions discovered incidentally on routine chest radiographs and measure from 0.7 to 6.5 cm.

The differential diagnosis of CCTL includes lung carcinoma, carcinoid tumour, granular cell tumour, acinic cell carcinoma, metastatic malignant melanoma, and metastatic renal cell carcinoma. These neoplasms can be discerned from CCTL by a combination of clinical presentation, physical examination, light microscopy, and histochemical and immunohistochemical stains. On histological examination, only CCTL demonstrates abundant intracytoplasmic glycogen, HMB-45 positivity, and negative staining for cytokeratin, chromogranin, and S-100 protein.\(^7,8\)

The histogenesis of CCTL remains uncertain. Liebow and Castleman favoured a myoid origin owing to the clear cell features of the tumour, which resembled clear cell leiomyomas of the uterus and stomach.\(^2\) This has been supported by reports of focal muscle-specific actin immunoreactivity,\(^11\) as well as ultrastructural studies which have demonstrated free
cytoplasmic glycogen, pinocytic vesicles, smooth endoplasmic reticulum and intracytoplasmic filaments, all of which support a myoid/pericytic origin. In addition, membrane-bound and intracytoplasmic electron-dense granules, as well as the full developmental spectrum of melanosomes, have also been identified in CCTL. Other investigators postulate neuroendocrine, metabolic, and epithelial derivations and base their conclusions on differing immunohistochemical and ultrastructural data. Clear cell neoplasms with morphological and immunophenotypic characteristics of CCTL have also been described in extrapulmonary sites and have been designated as ‘primary extrapulmonary clear cell “sugar” tumours’ (PEST). The majority of CCTLs follow a benign course with the exception of one case which featured necrosis and columnar cells, metastasized to the liver 10 years post-resection of the primary tumour and was eventually fatal. PESTs also appear to behave in a similar benign fashion to their pulmonary counterpart, although there was a case involving the serosa of the ileum which apparently pursued a malignant course. Recently, four cases of a malignant abdominopelvic tumour were also described in female patients with an age range of 19-41 years, histologically exhibiting the characteristic clear cell appearance with abundant cytoplasmic glycogen and strong immunoreactivity with HMB-45 antibody. Common to these four cases, but not seen in benign CCTL, were the presence of lymphovascular invasion, coagulative necrosis, and moderately pleomorphic nuclei. The term “perivascular epithelial cell” (PEC) was introduced by Bonetti et al. in 1992 for an unusual cell type present in angiomyolipoma and CCTLs, which is characterized by its epithelioid appearance, clear to eosinophilic cytoplasm, and perivascular distribution. The immunophenotype of this “PEC” is defined by strong immunoreactivity with HMB-45 antibody. Focal actin expression has also been noted, and although focal S-100 protein has been occasionally found in these cells, its expression has not been a consistent finding. These cells do not express cytokeratins. It has also been demonstrated that PEC shares features with melanocytes, neuroendocrine cells, and muscle cells. Ultrastructurally, PECs have abundant glycogen, well-developed rough endoplasmic reticulum, and numerous mitochondria. Subsequently, a group of lesions, including angiomyolipoma, CCTL, lymphangiomyoma, lymphangioleiomyomatosis, renal capsuloma and clear cell myelolipacytotic tumour of the ligamentum teres were found to share similar immunohistochemical, histological, and ultrastructural features and were characterized by the presence of this distinctive cell type, the PEC. This group of lesions has been designated as PEComas. Common to PEComas is the female preponderance, mainly young age group, and characteristic immunophenotype. PEComas have been recognized mainly in the kidney, liver, and lung, but are rapidly becoming a ubiquitous tumour.

Although most reported cases of CCTL were not investigated for stigmata of tuberous sclerosis (TSC), there have been reports of a CCTLs in female patients with TSC. The presence of intracytoplasmic pre-melanosomes, membrane-bound electron-dense granules, and immunohistochemical staining for HMB-45 in CCTLs are also shared by other non-melanocytic HMB-45 immunoreactive tumours seen in TSC such as lymphangioleiomyomatosis (LAM) and angiomyolipoma (AML). Consequently, it was proposed that that CCTL may be included in the family of TSC-related lesions. However, the inclusion of CCTL into TSC-related lesions is debatable, since unlike AML and LAM, CCTL has not been unequivocally shown to be of smooth muscle origin, or intimately associated with blood vessels or lymphatics. Also, the HMB-45 positivity may be an idiosyncratic reaction, as premelanosomes have not been identified in many of the ultrastructural studies of CCTL. Lastly, reports of clear cell “sugar” tumours of the rectum, heart, and pancreas, as well as sporadic cases of AML in individuals without TSC, raise additional questions and make associations between CCTL and TSC difficult to substantiate. It was concluded that further investigations, including cytogenetic and biochemical analyses, as well as immunoelectron microscopical studies of all these tumours, in addition to continued work towards identifying the TSC1 gene structure and function, and TSC2 gene function would be needed to verify the proposed associations.

CONCLUSION

We describe the first reported case of a clear cell “sugar” tumour of the lung (CCTL) in Malaysia. Although this entity is well recognized in the lung, pathologists need to be aware of its
existence and characteristic staining properties when considering differential diagnoses of lung lesions. Pathologists also need to be aware of its location in extrapulmonary sites. The behaviour of this tumour is difficult to predict, since although most have been reported to be benign, there exists reports of those which are associated with malignancy, histologically exhibiting lymphovascular invasion, necrosis, and pleomorphism. The possibility that CCTL may be related to lymphangioleiomyomatosis (LAM), angiomiyolipoma (AML), and part of tuberous sclerosis (TSC) also holds great interest. Increasing recognition of CCTL with further investigations will hopefully shed light on the behaviour, outcome and associations of this tumour.

REFERENCES