Disseminated large cell neuroendocrine carcinoma associated with ectopic adrenocorticotropic hormone secretion

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Introduction

Ectopic adrenocorticotropic hormone (ACTH) secretion is associated with a heterogeneous spectrum of neuroendocrine tumours (NETs) as well as non-NET tumours. Both ectopic ACTH secretion (EAS) and NETs are relatively uncommon. Large cell neuroendocrine carcinoma (LCNEC) is considered to be a poorly differentiated NET, and is very rarely associated with EAS. Only case reports of EAS associated with LCNEC have been documented. We present a case of disseminated LCNEC associated with EAS. The LCNEC was diagnosed on bone marrow trephine biopsy, and the likely but unproven primary was a NET arising from the superior mediastinum, which also caused superior vena cava (SVC) syndrome at presentation.

Case report

A 36-year-old black female presented with a four-month history of chronic coughing, constitutional symptoms and progressively worsening facial swelling that was especially noticeable in the mornings. She was human immunodeficiency virus-positive and in her fourth year of antiretroviral therapy. Tenofovir, lamivudine and efavirenz were the antiretroviral (ARV) drugs being taken. She had no history of ARV regimen changes. Prior to falling ill, her baseline CD4 count was 401 x 10^6 cells/l. On admission, her CD4 count was 139 x 10^6 cells/l with a suppressed viral load.

In the months prior to presentation, she had been attended by several healthcare professionals. Her sputum was negative for acid-fast bacilli. *Mycobacterium tuberculosis* was not detected on nucleic acid amplification testing [Xpert® *M. tuberculosis* (MTB)/resistance to rifampicin (RIF) assay]. Culture for *M. tuberculosis* was negative, and normal flora grew on bacterial culture.

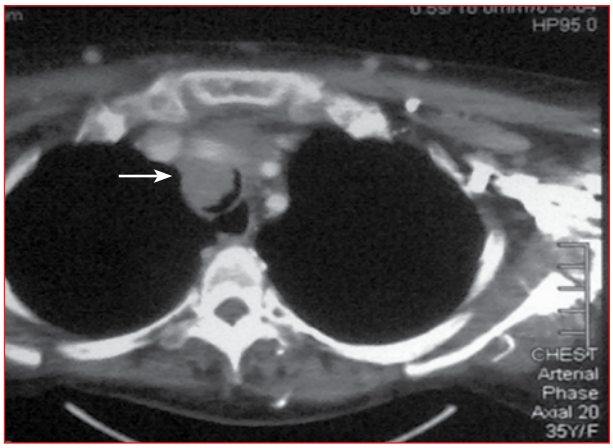

Figure 1: Computed tomography of the chest demonstrating superior mediastinal mass (arrow)

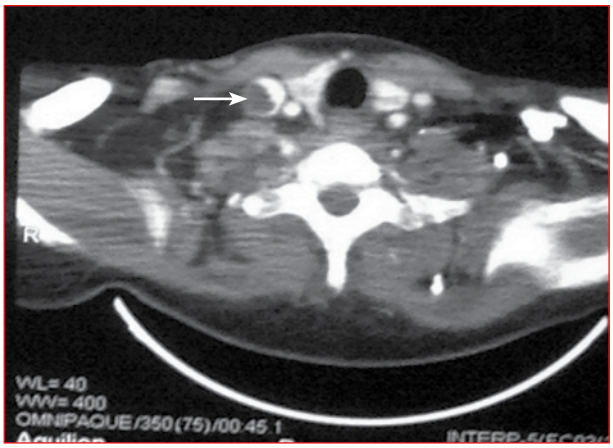

Figure 2: Computed tomography of the chest demonstrating thrombus in the right internal jugular vein (thick arrow) and lytic vertebral lesions (thin arrow)

At presentation, she also had an acute five-day history of pleuritic chest pain with increasing dyspnoea. Clinical findings supported a diagnosis of SVC obstruction and pneumonia involving the left lower lobe. Doppler flow studies confirmed a mural thrombus of the right internal jugular vein. Computerised tomography (CT)

(Figures 1 and 2) of the chest showed thrombus in the SVC extending into the right internal jugular vein 5 cm above the clavicle. A superior mediastinal soft tissue mass with dimensions 48 mm x 27 mm x 63 mm was noted. There was external compression of the trachea with > 50% narrowing. Encasement of the left main vessels, multiple collateral vessels, right hilar nodes, a pericardial effusion of 13 mm and bilateral small pleural effusions were observed. Patchy areas of ground glass changes in the lung parenchyma were seen. The left lung was more affected than the right. Radiologically, this was considered to be in keeping with infective changes. Diffuse mixed lytic and sclerotic vertebral lesions were reported. Sonar of the abdomen was normal. A transthoracic echocardiogram confirmed a 13-mm pericardial effusion and a structurally normal heart. The patient was commenced on a course of intravenous cefuroxime, to which she responded promptly. Anticoagulation was commenced with low-molecular-weight heparin and then warfarin was added. High-dose dexamethasone 8 mg thrice daily was started empirically as lymphoma was considered in the differential diagnosis. The patient's ARV drug regimen was continued.

The case was reassessed several days later and Cushing's syndrome diagnosed. In addition to the previously mentioned clinical features, central obesity, a round face, a supraclavicular dorsal fat pad and a dorsocervical fat pad were observed in the patient. Hyperpigmentation, oily skin, acne and easy bruising featured, as well as proximal myopathy. She was newly diagnosed with diabetes mellitus and hypertension, and had a metabolic alkalosis. The patient's relevant biochemical results are presented in Tables I and II. Because of SVC syndrome, she had received high doses of corticosteroids for seven days. Thus, a serendipitous high-dose dexamethasone suppression test had been performed prior to giving consideration to the diagnosis of Cushing's syndrome. Non-suppressible serum cortisol and urine cortisol levels were noted, as well as a significantly raised ACTH level.

Table I: Patient's serum biochemical findings on admission

Biochemical parameters	Value	Normal range
Potassium	2.4 mmol/l	3.3-5.3 mmol/l
Chloride	87 mmol/l	99-113 mmol/l
Bicarbonate	42 mmol/l	18-29 mmol/l
Calcium	2.21 mmol/l	2.05-2.56 mmol/l
HbA_{1c}	7.4%	< 6%

HbA_{1c}: haemoglobin A_{1c}

Table II: Patient's biochemical findings after seven days of high-dose dexamethasone

Biochemical parameters	Value	Normal range
24-hour urine-free cortisol	> 2 069 nmol/24 hours	58-807 nmol/24 hours
Random serum cortisol		
First measurement	> 2 069 nmol/l	119-618 nmol/l (07h00-09h00) 85-460 nmol/l (15h00-17h00)
Second measurement	689 nmol/l	
Third measurement	1 122 nmol/l	
Serum ACTH	104 ng/l	0-46 ng/l

ACTH: adrenocorticotropic hormone

Cushing's syndrome secondary to EAS was suspected. Ketoconazole was prescribed for medical control of the Cushing's syndrome pending a definitive histological diagnosis of the tumour. The pulmonology unit was consulted. It was determined that mediastinoscopy was relatively contraindicated in view of the SVC syndrome. The case was discussed with the radiology unit, and it was decided that the mass was not amenable to CT-guided fine-needle aspiration. A bone marrow aspirate and trephine biopsy were performed. The trephine biopsy showed very limited paratrabecular clusters of cohesive atypical cells displaying eosinophilic cytoplasm, oval nuclei and distinct nucleoli. The nuclear membranes were indistinct, and there was no cytoplasmic clearing or rosette formation. This infiltrate was present within less than 5% of the represented marrow. No overt small cell morphological features, necrosis or mitoses were evident in the limited areas of tumour infiltration. The tumour cells demonstrated immunoreactivity with pankeratin (AE1/AE3) and synaptophysin. Unfortunately, the tumour was no longer evident in subsequent sections, thus precluding further immunohistochemical staining (ACTH, parathyroid hormone, CD99, calcitonin and Ki-67). The findings were interpreted as metastatic carcinoma with neuroendocrine differentiation. LCNEC was favoured (Figures 3, 4 and 5). In support, the serum chromogranin A was elevated at 458.1 ng/ml (0-84.7 ng/ml).

The patient was subsequently transferred to the oncology unit where six cycles of cisplatin and etoposide were administered. After the fifth cycle of chemotherapy, a CT scan of the chest was performed. The tumour had reduced in volume by 34.4%. There was complete obstruction of both the right and left brachiocephalic veins. The tumour had clearly invaded the trachea. In the anterior segment of the right upper lobe, a peripheral nodule, together with

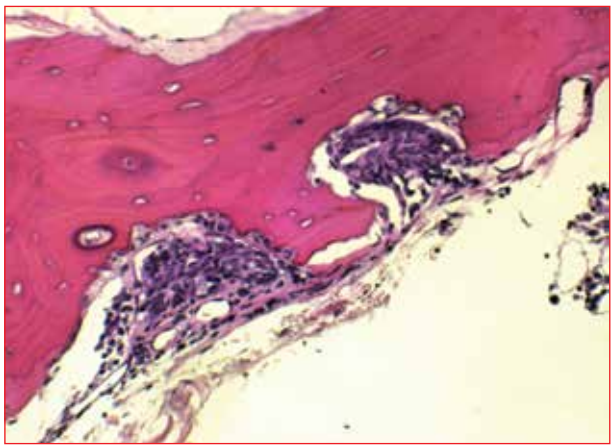

Figure 3: Haematoxylin and eosin-stained section of bone marrow displaying paratrabecular infiltration by atypical cohesive tumour cells (x 200 magnification)

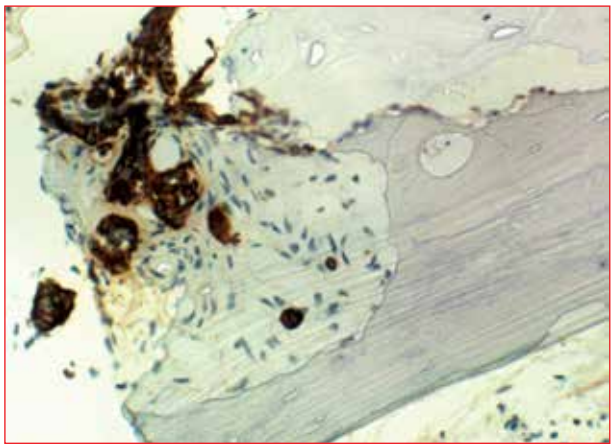

Figure 4: Immunohistochemistry with pankeratin (AE1/AE3). There is diffuse cytoplasmic and membrane immunoreactivity within the metastatic tumour cells

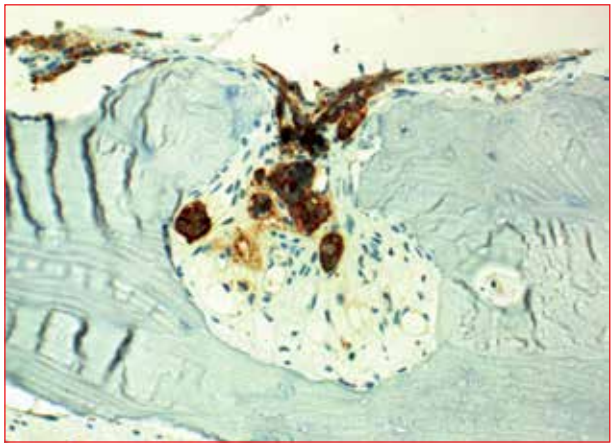

Figure 5: Immunohistochemistry (synaptophysin). There is diffuse cytoplasmic staining in the tumour cells

a tree-in-bud appearance, was observed. This is in keeping with endobronchial spread. Multiple significant right paratracheal, right hilar and subcarinal lymph nodes were noted. The bone lesions in the thoracic vertebrae were still present. In addition, there was an intramedullary soft tissue mass involving the sternum. Radiologically, this was consistent with metastatic disease. The patient was evaluated for mediastinal irradiation in an attempt to ameliorate her locally invasive and compressive disease.

Discussion

Causes of Cushing's syndrome can be divided into those that are ACTH dependent and those that are ACTH independent. ACTH-dependent causes are approximately four times more common than ACTH-independent causes. EAS accounts for 12% of all cases of Cushing's syndrome, and 20% of ACTH-dependent causes.[1,2] EAS is not common, the exact incidence is not well documented, and the data are limited to small series and case reports.[2-4] EAS has been documented in association with a heterogeneous group of NETs, as well as non-NETs arising from diverse primary sites. The most common tumours associated with EAS are bronchial carcinoid, small cell lung carcinoma, gastroenteropancreatic neuroendocrine, thymic neuroendocrine carcinoma, medullary thyroid carcinoma (MTC) and phaeochromocytoma.[2,3] Disseminated NECs of unknown primary account for 6.5% of cases.[3]

NETs account for no more than 0.5% of all malignancies.[5] The diversity of primary sites that harbour NETs, the expression of humoral factors, tumour differentiation, tumour grade and the presence or absence of disseminated disease have complicated the classification of NETs.

Recently, there has been a concerted effort to classify NETs more comprehensively. Several classification systems exist, but they share many common features.[6] Strong emphasis is placed on tumour differentiation, which describes the degree to which neoplastic cells resemble non-neoplastic cells. A clear distinction is made between well differentiated and poorly differentiated tumours. The grade is also important as it defines the biologic aggressiveness of the tumour. It is assessed by determining the proliferative rate, which can be measured by the Ki-67 marker or by the number of mitoses per unit area of tumour. Some systems also use the presence of necrosis to determine the grade. NETs are divided into low, intermediate and high grade. The present World Health Organization (WHO) system uses tumour histology, size, the involvement of adjacent tissue, angioinvasion, mitoses per unit area, the proliferation index (Ki-67) and metastatic disease in classifying NETs.[7,8] The WHO classification is useful in predicting prognosis and assists with guiding the selection of appropriate therapy.[8-10] NECs of unknown primary, like NETs of specific organs, are either well differentiated or poorly differentiated (Table III).[5,11]

Primary thymic neuroendocrine carcinoma (NEC), MTC, primary thyroid nonmedullary cell NEC, paraganglioma, primary lung LCNEC and lymphoma tumours need to be considered in the context of a patient with a superior mediastinal mass and EAS.[2,12]

The most common primary NET located in the mediastinum is thymic in origin.[13] Thymic NECs have been well documented in case series.[12,14,15] Thymic NECs tend to display greater cytologic atypia and generally have a more aggressive nature than carcinoids that arise elsewhere. Thus, the term "thymic NEC" is preferred to the older term "thymic carcinoid".[12] Thymic NECs are associated with EAS in 6% of cases and with SVC obstruction in 2%.[12] Thymic NECs associated with EAS tend to be well differentiated (low- or intermediate-grade).[14,15] There is evidence to suggest that well differentiated thymic NECs may evolve into poorly differentiated thymic NECs, but with small cell, rather than large cell, morphology.[12] Primary thymic LCNEC is rare and is limited to case reports.[16] Primary thymic LCNEC that is associated with EAS is very rare. To the best of our knowledge, one case report documents a primary thymic LCNEC associated with EAS.[17] A second case report documents an unspecified poorly differentiated thymic NEC associated with EAS.[18]

MTC is a well known cause of EAS and accounts for 5.5% of cases.[3] Our patient had a serum procalcitonin of 0.06 µg/l (normal value in health < 0.5 µg/l). Serum procalcitonin has a sensitivity of 91% and a specificity of 96% for MTC.[19] Thus, MTC was considered to be less likely, but not impossible.

To the best of our knowledge, there is one case report of a primary thyroid nonmedullary cell NEC with small cell morphology associated with EAS.[20] However, no cases of primary thyroid nonmedullary cell LCNEC were found in the literature. Again, to the best of our knowledge, there is only one reported case of a superior mediastinal paraganglioma associated with EAS, and only one reported case of primary lung LCNEC associated with EAS.[21,22] No case of superior mediastinal lymphoma associated with EAS was found in the literature. Thus, poorly differentiated NEC with large cell morphology associated with EAS arising from the superior mediastinum is rare.

The prognosis in NEC of unknown primary strongly relates to histological differentiation, proliferative activity and the presence of metastatic disease, rather than the site of the primary lesion. NEC grade 3 has a median survival of five months. Survival at five years is only 5%.[23]

Treatment options for poorly differentiated NEC grade 3 are limited. Recent guidelines recommend treatment with cisplatin and etoposide. As yet, there is no established second-line therapy.[23] The treatment armamentarium is expanding for well differentiated NETs, but this discussion is beyond the scope of this report.

Table III: Classification of unknown primary neuroendocrine tumour or carcinoma[6,8,11]

Differentiation	Grade	WHO/ENETS
Well differentiated	Low	Neuroendocrine tumour (grade 1)
	Intermediate	Neuroendocrine tumour (grade 2)
Poorly differentiated	High	Neuroendocrine carcinoma (grade 3, small cell)
		Neuroendocrine carcinoma (grade 3, large cell)

ENETS: European Neuroendocrine Tumor Society, WHO: World Health Organization

Surgery remains the treatment of choice for all causes of endogenous Cushing's syndrome.[24,25] Medical therapy is indicated in preparation for surgery in patients who are not fit for surgery, in patients where surgery is not an option (e.g. unresectable tumours, metastatic disease and tumours of unknown primary), and in patients who remain hypercortisolemic postoperatively. Current medical treatment options include suppression of adrenal steroidogenesis with ketoconazole, metyrapone, etomidate or mitotane. Cabergoline, a centrally acting dopamine receptor agonist, suppresses ACTH secretion in some patients and is used off label. Octreotide, a somatostatin agonist, is purportedly effective in EAS and is also used off label. Mifepristone, a glucocorticoid receptor antagonist, has also recently been added to the list of treatment options.[25] Other agents are being investigated as well.

In conclusion, we describe a case of disseminated LCNEC associated with EAS diagnosed on bone marrow trephine biopsy. Unfortunately, owing to the very limited tumour infiltration within the sampled bone marrow, ACTH and other immunohistochemistry was not possible. The patient presented with SVC syndrome and a CT showed a superior mediastinal mass. We were unable to obtain a tissue specimen of this superior mediastinal mass. Irrespective of the exact nature of the suspected primary arising from the superior mediastinum, disseminated LCNEC associated with EAS is very rare, and unfortunately has a poor prognosis.

Conflict of interest

The authors have no conflict of interest to declare.

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