Patient with respiratory distress, facial oedema and refractory hypokalaemia

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SUMMARY
Small cell lung carcinoma, when associated with co-occurrence of complications such as paraneoplastic syndrome and superior vena cava syndrome, poses a greater management challenge to the clinical team. We report a 56-year-old man who was eventually diagnosed with stage III small cell lung carcinoma, presenting with respiratory distress, facial and upper body oedema, proximal muscle weakness, hypokalaemia, new-onset hypertension and hyperglycaemia. His medical management was complicated by associated superior vena cava syndrome and Cushing’s syndrome leading to refractory hypokalaemia, immunosuppression and depression. Although the patient improved clinically and biochemically with the chemotherapy and other treatments, the development of neutropenic pneumonia led to his demise. This case highlights the importance of a multidisciplinary approach to achieve better patient care and the need for good clinical vigilance to identify possible humoral manifestations of aggressive malignancies such as small cell carcinoma of the lung to assist their early detection.

BACKGROUND
Small cell lung carcinoma (SCLC), also known as oat cell lung carcinoma, is a subtype of primary lung malignancies due to inhaled carcinogens, with cigarette smoking being the key culprit. They are highly malignant tumours that rapidly grow and widely metastasise and, despite being responsive to chemo/radiotherapy initially, have a poor prognosis.1 SCLC commonly results in necrosis, superior vena cava syndrome (SVCS) and paraneoplastic syndromes (PNS) such as hypercalcaemia of malignancy, syndrome of inappropriate antidiuretic hormone secretion and ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS).1 2 These paraneoplastic manifestations may provide valuable clues for the early diagnosis to a vigilant observer, whereas it can also pose a diagnostic challenge if miscorrelated.

EAS is observed in 1%–5% of the SCLC cases, while SCLC is the most common extrinsic cause of SVCS with 10% of the patients developing SVCS at some point.3 4 EAS can be considered an endocrine emergency due to the acuteness and severity of its manifestations owing to the rapid development of severe hypercortisolism, while SVCS is considered as an oncological emergency due to its life-threatening nature, although it is not fatal in a majority.3 6 SCLC associated with both of these syndromes can pose a significant challenge to the clinical team due to implications caused by each of them and the primary malignancy itself, as observed in this case reported by us.

CASE PRESENTATION
A 56-year-old Asian man admitted with a 3-month history of worsening respiratory distress, proximal muscle weakness, hyperpigmentation, significant loss of weight (10 kg) and apathy. He did not have any fever, sputum or haemoptysis. He had developed facial swelling in the last 1 month, which had gradually progressed to upper limbs and chest with a worsening headache.

The clinical examination revealed prominent upper body swelling, including face, neck, chest and upper limbs with skin plethora and prominent neck and upper body veins. He also had hyperpigmentation of the face and hands (figure 1). The patient was cachectic with a low body mass index (18.1 kg/m²) despite significant oedema. He had severe hypertension with a blood pressure of 180/100 mm Hg (heart rate: 88 beats/min), moderate respiratory distress and reduced proximal muscle power in all four limbs. Until 3 months back, he was healthy and not on any medication. There was no family history of metabolic disorders or malignancy. He had a history of more than 25 pack years of smoking.

INVESTIGATIONS
His initial biochemical investigations revealed severe hypokalaemia, hyperglycaemia and mild hypocalcaemia (table 1). The hypokalaemia was refractory to intravenous KCl infusion. When he presented to his local hospital with cough 2 months back, he was found to have mild hypokalaemia (2.9 mmol/L) which had responded to oral potassium replacement, due to which it was not further investigated.

The chest radiograph taken for the evaluation of his respiratory distress revealed a mass lesion in the right hilar region, which was identified as a lobulated solid soft-tissue mass (11.7×5.7×4.7 cm) at the right hilar region that could not be differentiated from the enlarged right hilar nodes by contrast-enhanced CT scan (T4N2M0—stage IIIb; figure 2). The finding of severely stretched proximal superior vena cava with luminal narrowing on CT scan (figure 2D) confirmed the diagnosis of SVCS. The patient was immediately started on prophylactic intravenous dexamethasone to relieve any laryngeal and cerebral oedema. The cytological examination of bronchial brushing indicated atypical cells with nuclear atypia (figure 3A), while...
histological examination of the bronchial biopsy confirmed the diagnosis of SCLC (figure 3B,C).

Meanwhile, further investigations carried out to identify the cause of refractory hypokalemia revealed metabolic alkalosis and urinary potassium wasting. The finding of raised 9-am serum cortisol level with increased ACTH level unveiled the possible source of the biochemical picture as ACTH dependent hypercortisolism (table 1). In the presence of ACTH dependent Cushing’s syndrome, the next level of the diagnostic workup would be dynamic endocrine tests for the differentiation between pituitary and ectopic ACTH secretion. However, none of the dynamic endocrine tests was necessary for this patient providing an unorthodox approach to the diagnosis. He had been on high-dose intravenous dexamethasone for 2 days at the initial blood sampling for basal cortisol. Thus, the initial 9 am cortisol value was a result equivalent to, or even more intense suppression than a high-dose dexamethasone-suppression-test (HDDSST). Therefore, unsuppressed cortisol by exogenous glucocorticoids was suggestive of ectopic ACTH secretion. Although bilateral inferior petrosal sinus sampling (BIPSS) is considered the gold standard for the localization of ACTH secretion, it was not clinically appropriate for our patient due to severe comorbidities. Instead, the source of ACTH was ascertained by establishing the neuroendocrine nature of SCLC cells. The bronchial biopsy was strongly positive for chromogranin (figure 3D) and synaptophysin (figure 3E). Intense immunohistochemical staining of the bronchial biopsy for ACTH confirmed the origin of the ACTH as SCLC in our patient (figure 3F).

Differential Diagnosis

During the initial investigation for the hypokalaemia and hypertension; uncontrolled essential hypertension with diuretic use, primary/ secondary hyperaldosteronism (renovascular hypertension, malignant hypertension, reninoma), Liddle’s syndrome, and hypokalaemic thyrotoxic periodic paralysis were also considered as possible differential diagnoses. Although the pathophysiology of hypokalaemia, hypertension and hyperglycaemic could be explained by the hypercortisolism alone, thyrotoxicosis was actively excluded by investigation (table 1).

Treatment

With the diagnosis of SVCS, the patient was directed for urgent chemotherapy with etoposide (120 mg daily given intravenously for 5 days) and cisplatin (70 mg given intravenously on the day one). The SVCS responded to treatment with complete reduction of upper body oedema and settling of respiratory distress within 5 days of treatment. The patient was started on spironolactone and intravenous KCl for hypokalaemia, ketoconazole for steroidogenesis inhibition and prophylactic antibiotics. The serum cortisol level reduced to 213 nmol/L from the initial value of 1640 nmol/L, indicating good response to the treatment initially. The patient was also provided with psychological counselling and treated with antidepressants due to moderate depression.

Table 1  Summary of investigation findings of interest

| Parameter                        | Value       | Reference limits |
|----------------------------------|-------------|-----------------|
| Electrolytes                     |             |                 |
| Sodium                           | 138 mmol/L  | 135–145         |
| Potassium                        | 2.1 mmol/L  | 3.5–4.5         |
| Total calcium                    | 1.99 mmol/L | 2.2–2.7         |
| Metabolic parameters             |             |                 |
| Random glucose                   | 323 mg/dL   | <200            |
| Fasting glucose                  | 130 mg/dL   | 60–100          |
| Parameters of acid base balance  |             |                 |
| pH                               | 7.63        | 7.35–7.45       |
| pCO₂                             | 35.2 mm Hg  | 35–45           |
| Bicarbonate                      | 37.7 mmol/L | 22–26           |
| Base excess                       | 16.2 mmol/L | (−2) – (+2)     |
| Hormonal assays                  |             |                 |
| 9-am cortisol                    | 1640 nmol/L | 138–635         |
| ACTH                             | 285 pg/mL   | 10–60           |
| Thyroid stimulating hormone      | 1.050 mIU/L | 0.465–4.68      |
| Urinalysis                       |             |                 |
| Spot urinary potassium           | 31 mmol/L   | <15             |
| Potassium/creatinine ratio       | 3.5 mmol/mmol | <1.5      |
| Fractional excretion of potassium| 8.50%       | 4%–16%          |

ACTH, adrenocorticotrophic hormone.
OUTCOME AND FOLLOW-UP
With a multidisciplinary management approach, the patient became clinically and psychologically stable as the clinical symptoms of SVCS and hypercortisolism-induced comorbidities subsided with treatment. However, he developed severe neutropenia following completion of the chemotherapy, which progressed to severe pneumonia and expired after 10-days. Although the patient had been having clinical symptoms for more than 3 months, since the diagnosis of SCLC was confirmed only 3 weeks back, the demise of the patient became a sudden loss for his relatives and created a significant psychological impact on the family, especially on his wife.

DISCUSSION
SCLC is a highly malignant tumour accounting for 15% of lung cancers with 7% 5-year survival.1 Their poor prognosis is a collective result of their aggressive nature, associated syndromes such as PNS and SVCS owing to the distinct pathological, clinical and molecular characteristics of SCLC.1 2

PNS is a collection of clinical manifestations that are not directly caused by the primary malignancy or its metastasis but arises due to functional peptides or hormones secreted by the tumour or inappropriate immune reaction initiated by the tumour.7 SCLC is a neuroendocrine tumour with the potential to secrete such functional mediators leading to paraneoplastic manifestations such as EAS.5 When the clinical presentation of paraneoplastic manifestations precedes that of the primary malignancy, it can contribute to the early diagnosis of primary malignancy.5 EAS secondary to SCLC rarely exhibits all classical features of Cushing’s syndrome, especially those due to fat redistribution.8 As a result of the aggressive nature of SCLC, the short duration of exposure to hypercortisolism does not permit adequate time for such changes to occur.10 However, almost all patients exhibit humoral effects of cortisol such as hypokalaemia, sodium and water retention leading to hypertension.11 Keeping with these observations, our patient also presented with humoral effects such as hypokalaemia, hyperglycaemic, hypertension, and weight loss instead of obesity, indicating rapid development of Cushing’s syndrome and prominence of the primary malignancy. Further, EAS contributes to poorer prognosis due to the advanced stage at presentation and increased susceptibility to infection as a consequence of hypercortisolism.9 12

The diagnostic workup for EAS begins with the establishment of hypercortisolism, which usually poses no difficulty given the severity of hypercortisolism.5 It is based on 24 hours urinary free cortisol assay and/or serum cortisol and ACTH levels in several samples, followed by dynamic endocrine tests to establish the source of ACTH as not from the pituitary. The recommended tests include corticotrophin-releasing hormone (CRH)/desmopressin stimulation tests both of which are based on the pronounced expression of respective receptors by pituitary adenomas leading to the excessive release of ACTH in the presence of a pituitary pathology.3 An HDDST can be used to demonstrate suppression of cortisol secretion by exogenous glucocorticoids observed in pituitary pathology, whereas EAS is resistance to such suppression. These tests should be carried out in the presence of active hypercortisolism to obtain interpretable results. As our patient was already on high-dose dexamethasone at the baseline measurement of cortisol, >50% suppression from the basal level, could not be demonstrated as per the guidelines. Because the cortisol level was three times the upper-limit-of-normal in the presence of potent feedback inhibition, it was clinically reasonable to accept it as equivalent to a non-suppressed HDDST. BIPSS combined with CRH/desmopressin is considered the ‘gold standard, for differentiating EAS from ACTH secreting pituitary adenomas. Instead of employing this invasive investigation, we used the immunohistochemical staining of the tumour biopsy for ACTH to confirm the origin of ACTH as ectopic to the pituitary. These findings led to an unorthodox diagnostic approach to EAS in this patient.

The SVCS as observed in our patient, occurs due to either extrinsic or intrinsic compression of the venous return from the head and neck region while the pace of the onset of venous restriction being the principal cause for the development of SVCS. It causes swelling of the face, neck, upper limbs and chest. The resultant oedema can debilitate the larynx and pharynx contributing to dyspnoea, hoarseness and dysphagia. It is a considered as an oncological emergency and can be potentially life-threatening necessitating immediate chemoradiation.

From the therapeutic viewpoint, the clinical team has to identify the of tumorous and hormonal risks which are essential to direct the management plan often requiring multidisciplinary input. Chemotherapy with etoposide and cisplatin or carboplatin can potentially act by the cessation of cytochrome P450 steroidogenic enzymes, whereas ideal management being surgical resection of the tumour. Apart from the management of hypokalaemia, hypoglycaemia and immunosuppression, the patient may require psychological assistance and antidepressants as observed in our patient. Most patients with EAS due to SCLC present at an advanced stage with poor response to chemotherapy and sepsis being the leading cause of death due to immunosuppression, which was also observed in our patient.10 12

As evident by the index case, SCLC complicated by EAS and SVCS poses a great challenge to the clinical team due to the
Patient’s perspective

Following is the English translation of the narrations in Sinhala by the patient and his wife.

Patient (during the last few days of his life before his demise): “I am happy that my disease was detected within less than two weeks during this admission. I can accept the consequences of this cancer as they are the result of my own doing. I hope I will at least have a few months to settle everything at home. My wife is completely dependent on me. After that, I can die in peace.”

Patient’s Wife (six months after the death of the patient): “I still cannot believe he left us. He was a very caring husband. He was always worried about his unfinished duties during his last days. We don’t have much financial difficulty, but I always remember my husband as he was always there for me. I cannot believe that he died as it was only two weeks since this cancer was diagnosed. We thought he only had a cough and lung infection previously. We didn’t even inform any of our relatives about the disease. I would have been happy if he at least had a few months, then he could have fulfilled some of his work.”

These comments highlight the need for closure is just as vital as being cured of a disease.

Learning points

- Co-occurrence of superior vena cava syndrome and ectopic adrenocorticotrophic hormone (ACTH) syndrome poses a significant management challenge.
- Doctors should have good clinical vigilance to identify humoral manifestations of aggressive malignancies such as small cell carcinoma of the lung to assist their early detection.
- Ectopic ACTH secretion from tumour can be confirmed by immunohistochemical staining of the tumour biopsy in place of invasive bilateral inferior petrosal sinus sampling.

aggressive nature of the tumour, humoral effects and immunosuppression exerted by hypercortisolism, potential oncological emergency created by SVCS, and psychological disturbances caused by the knowledge of having a malignancy itself aggravated by psychological effects of hypercortisolism. Thus, the best possible management can only be achieved by a multidisciplinary approach to patient care, including respiratory physician, histopathologist, chemical pathologist, oncologist, general physician and psychiatrist working together for early diagnosis and provide medical and psychological management.

However, unexpected deaths that occur suddenly and earlier than expected, causing significant emotional impact, especially on the family members, cannot be prevented. Such deaths significantly impact the wholistic patient care including irresolution and unrealised dreams among patients and complicated bereavement among family members. Although unable to provide complete remission, the early diagnosis of an aggressive disease can provide the patient more time for acceptance and adjustment. Therefore, this case further highlights the importance of clinical vigilance for early detection of possible humoral manifestations of PNS that may precede the clinical presentation of the primary malignancy contributing to the early diagnosis of aggressive malignancies such as SCLC. Early diagnosis of aggressive malignancies would allow the clinical team to provide more time for the patients and their families to avoid the calamity caused by sudden death.

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