

Swollen Limbs and Bone Pain: A Case Report

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Abstract

A 50 year old man presented with peripheral oedema, abdominal distension and a pulmonary opacity on CXR. He subsequently perforated his sigmoid colon as a complication of diverticulitis with pericolic abscess. After colectomy his post-operative period was marked by severe hypokalaemia, metabolic alkalosis, hyperglycaemia and recurrent chest infections. Paraneoplastic Cushing's syndrome was diagnosed after finding elevated serum cortisol and ACTH levels. CT-guided biopsy of the lung lesion revealed small-cell carcinoma. Bone scan disclosed collapse of numerous thoracic vertebrae possibly due to osteoporosis or oncogenic osteomalacia. Treatment with steroid-synthesis blockers was commenced but the patient died before tumour-directed therapy could be started. Ectopic ACTH syndrome and oncogenic osteomalacia are discussed.

Learn to see in another's calamity the ills which you should avoid.

Publilius Syrius, *Sententiae*
(c. 100 BC)

Keywords

ACTH syndrome, ectopic, carcinoma, small cell, case report, cushing's syndrome, hypokalaemia, lung neoplasms, osteomalacia, paraneoplastic syndromes

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Case Report

A 50 year old drydocks worker was referred to St. Luke's Hospital with pitting lower limb oedema. His main complaint was a fifteen day history of ankle swelling and abdominal distension for which his family doctor had initially prescribed an amiloride hydrochloride 5mg - hydrochlorothiazide 50mg combination (Moduretic®). This medication had been discontinued four days prior to his first visit.

The medical history was unremarkable but for a spontaneous left pneumothorax at 35 years of age which was managed conservatively. The patient had a long history of cigarette smoking, having smoked around 20 cigarettes per day since the age of 16 years.

On examination, he looked well, was eupnoeic at rest and afebrile. There was no jaundice, pallor, finger clubbing or palpable lymph node enlargement. Pulse rate was regular at 80 beats per minute and blood pressure was 130/80 mmHg. Heart sounds were normal and the jugular venous pressure was not elevated. Chest auscultation was unremarkable. The abdomen was slightly distended: there was shifting dullness, 5 centimetre smooth hepatomegaly and a palpable tip of spleen. Digital rectal examination revealed normal stool and there were no mucosal lesions or prostatic nodules. He was also noted to have hyperpigmented skin however his wife maintained that she had always known him to have skin of this tinge.

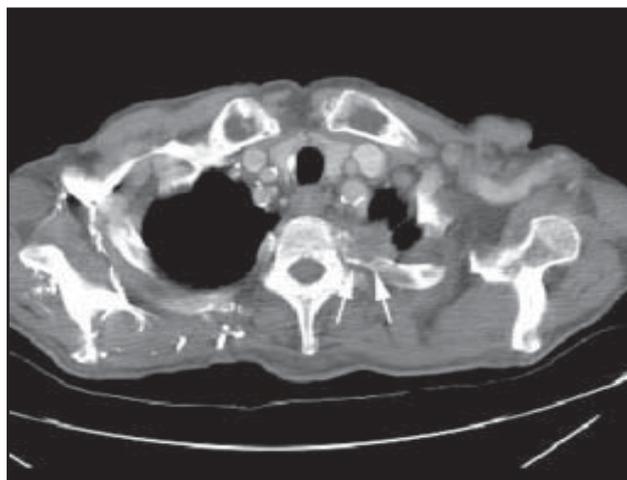


Figure 1: Computed tomography of thorax showing tumour eroding rib (arrows)

Table 1: Initial investigations

Haemoglobin (gm/dL)	14.3
White-cell count (per mm ³)	12 340
Neutrophils (%)	80.3
Platelets (per mm ³)	223 000
Erythrocyte sedimentation rate (mm/hr)	7
Urea (mmol/L)	3.8
Creatinine (µmol/L)	70
Glucose fasting (mmol/L)	5.49
Bilirubin (mmol/L)	16.3
Alkaline phosphatase (U/L)	249
Gamma glutamyl transferase (U/L)	28
Alanine aminotransferase	46
Albumin (g/L)	39.1
Sodium (mmol/L)	140
Potassium (mmol/L)	3.07
Chloride (mmol/L)	107
Calcium (mmol/L)	2.17
Phosphate (mmol/L)	0.9
Uric acid (µmol/L)	208
Thyroid stimulating hormone (U/L)	0.41
International normalised ratio	1.0
Urinalysis and microscopy	Normal
Electrocardiogram	Normal sinus rhythm

Table 2: Pre-op investigations

Haemoglobin (gm/dL)	16.2
White-cell count (per mm ³)	14 800
Platelets (per mm ³)	228 000
Urea (mmol/L)	7.3
Glucose fasting (mmol/L)	6.4
Sodium (mmol/L)	143
Potassium (mmol/L)	2.5
Arterial pH	7.504
HCO ₃ ⁻ (mmol/L)	36.9

Table 3: Further investigations

24 hour urinary K ⁺ (mmol/day)	104	(5-250)
Serum aldosterone (pg/mL)	96	(12-150)
Plasma renin activity (ng/mL/h)	3.68	(0.98-4.18)
Serum cortisol 9am (nmol/L)	>1380	(138-690)
24 hr urinary cortisol (nmol/L/day)	>1536	(55-276)
ACTH (pg/mL)	349	(<46)

Initial screening investigations are shown in Table 1. A chest radiograph showed an inhomogenous opacity with ill-defined outlines at the left apex. There was no hilar lymphadenopathy. Abdominal ultrasonography showed an enlarged liver without any focal lesions; the gallbladder, spleen and kidneys were reported as normal and no free fluid was detected in the abdomen. On computed tomography of the thorax a mass was identified in the posterior segment of the upper lobe subpleurally with extension to the chest wall and destruction of the adjacent rib (Figure 1). Significant fibrotic changes were noted in the same lobe. There was no mediastinal lymphadenopathy, pleural, or pericardial effusion.

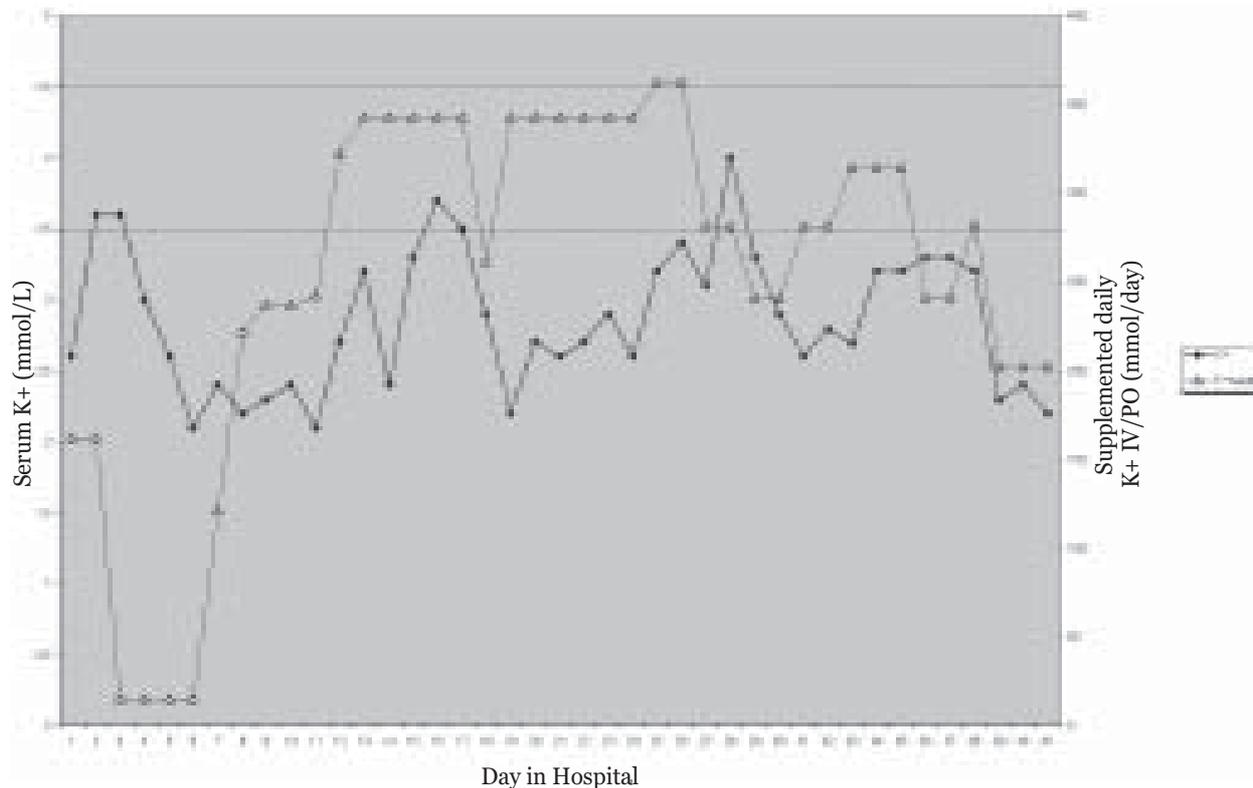
The patient was admitted for fibreoptic bronchoscopy. Widespread inflammatory changes in keeping with early chronic obstructive pulmonary disease were noted. No intrabronchial lesions were identified. Brush biopsies from the left upper lobe bronchus were submitted and reported negative for malignant cells. Bronchial lavage samples were sent for cytology, Ziehl-Neelsen staining and culture.

Haemophilus influenzae was identified and treated however other tests were normal. During his admission, the patient complained of further abdominal distension. Paracentesis at the right iliac fossa did not yield any fluid. At this point the patient was discharged with a follow-up appointment for bronchoscopy sample results.

Nine days after discharge, he presented to the Accident and Emergency department with severe abdominal pain and worsening abdominal distension. He had been taking diclofenac for left shoulder pain over the previous few days. Physical examination on admission showed a distended abdomen suggestive of ascites and signs of peritonitis. A chest radiograph disclosed air under the diaphragm. Pre-op investigations taken soon after arrival at A&E are given in Table 2. An urgent laparotomy was performed. At surgery, there was perforation of the sigmoid colon together with a pelvic abscess. No gross abnormalities were detected on direct visualisation of the liver, stomach, duodenum, spleen, gallbladder and kidneys. Partial sigmoid colectomy was performed with fashioning of an end colostomy in the left iliac fossa together with routine appendectomy. The resected specimens were submitted for histology and were reported as "periappendicitis, sigmoid colon segment with multiple diverticuli and some serosal inflammation". *Streptococcus constellatus*, *Escherichia coli*, and *Bacteroides fragilis* were cultured from peritoneal fluid samples.

The post-operative period, initially in the ICU and subsequently in a surgical ward, was marked by severe refractory hypokalaemia requiring massive doses of potassium replacement. Figure 2 shows his daily serum potassium level and the amount of potassium administered in various forms over the days he remained in hospital. Despite the large doses given, serum potassium was rarely within the physiological range (dotted lines). Hypokalaemia was initially attributed to gastrointestinal losses following bowel resection, however the unusual severity and persistence prompted further

Figure 2: K⁺ levels and K⁺ Supplementation during hospital stay



investigations (Table 3). These pointed to a diagnosis of hypercortisolism secondary to increased ACTH production.

During this period, the patient developed a hospital-acquired pneumonia which proved difficult to treat and he was given successively meropenem, piperacillin, clarithromycin and levofloxacin. Sputum studies were negative for acid-fast bacilli but *Alcaligenes xylosoxidans* was subsequently isolated. Apart from potassium supplementation and antibiotics, the patient was being treated with nebulised bronchodilators, diuretics including spironolactone due to his lower limb oedema and insulin as he eventually developed hyperglycaemia. Once it was

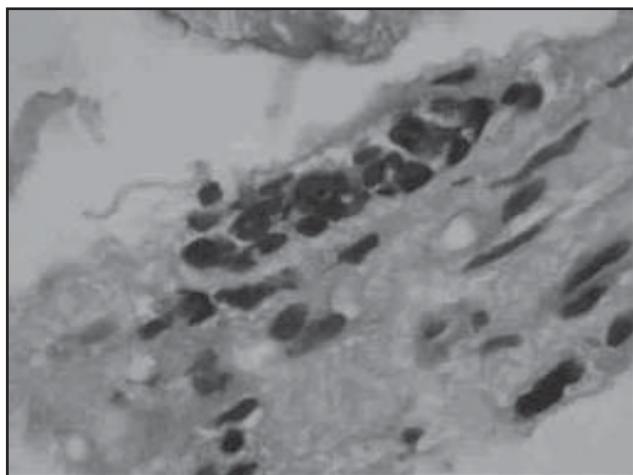


Figure 3: CT-guided specimen histology showing the typical hyperchromatic cells with scanty cytoplasm found in small cell lung carcinoma

established that the patient had hypercortisolism, a cortisol biosynthesis inhibitor was added to his treatment regime. Metyrapone 50mg TDS lowered serum cortisol to 444nmol/L after 5 days. When patient's clinical condition became more stable, a computed tomography-guided biopsy of the left lung lesion was performed. Histological examination of the biopsy specimen confirmed a diagnosis of small-cell carcinoma (Figure 3). Further work-up included computed tomography of the brain which was normal, and a bone scan which showed increased tracer uptake suggestive of vertebral collapse in T4, T7 and T9 to T11 vertebrae. It was suggested that these were features of a diffuse bone disease rather than metastases.

Three and a half months after his initial presentation, the patient suddenly developed severe dyspnoea and a clinical diagnosis of tension pneumothorax was made. An urgent thoracocentesis was performed with complete lung re-inflation. Despite this, the overall clinical condition rapidly deteriorated and the patient died soon after.

Discussion

The association between non-pituitary tumours and Cushing's syndrome was first reported by Brown in 1928.¹ Small-cell lung cancer is characterised by numerous paraneoplastic syndromes and ectopic secretion of corticotropin (ACTH) is one of the rare complications, being found in less than 5% of patients with this disease.²⁻⁴

ACTH and other pituitary peptides are synthesised from a common high molecular weight precursor pro-opiomelanocortin (POMC), which is cleaved to pro-ACTH and subsequently the active ACTH 1-39. Although POMC

Table 4: Types of tumour causing ectopic ACTH

Small cell lung cancer
Bronchial carcinoid
Other carcinoid tumours (thymus, small intestine)
Pancreatic islet cell tumour
Phaeochromocytoma
Medullary carcinoma of thyroid
Carcinomas (breast, GI tract, ovarian, cervical, prostate)

Table 5: Frequency of clinical features of ectopic ACTH syndrome associated with small-cell lung cancer⁸

Symptom	%
Peripheral oedema	83
Proximal myopathy	61
Moon face	52
Truncal obesity	35
Hyperpigmentation	22
Psychosis	22
Hypertension	22
Ecchymoses	17
Hirsutism	4
Striae	4

Table 6: Steroid-synthesis blocking therapy in ectopic ACTH syndrome

Drug	Mechanism of action
Metyrapone	Inhibition of 11beta-hydroxylase
Ketoconazole	Inhibition of cortisol synthesis
Aminoglutethimide	Inhibition of cholesterol conversion to pregnenolone
Octreotide	Inhibition of ACTH secretion
Etomidate	Adrenolytic
Mitotane	Adrenolytic

transcription occurs predominantly in the pituitary, low level expression has been detected in a variety of other tissues.⁵ Many different types of tumours have been found to contain immunoreactive ACTH and other POMC-derived peptides.^{5,6} However, the actual incidence of secretion of excess ACTH is much less common – probably related to the absence of an essential signal sequence for translocation in peripheral cell mRNA.⁷ Table 4 lists the types of tumour associated with ectopic ACTH secretion. It is postulated that in these types of malignancy, changes in gene promoter regions or proliferation of cells producing the longer POMC mRNA enable secretion of active ACTH.

Refractory hypokalaemia was a prominent feature of the case reported. The clinical features of ectopic Cushing's syndrome show a number of differences from the classical symptom complex and often metabolic abnormalities may be the only manifestations. Hypokalaemia, usually associated with metabolic alkalosis, is present in more than 90% of patients with ectopic ACTH, compared to an incidence of 10% in Cushing's syndrome due to other aetiologies.⁸ The characteristic hypo-kalaemia is caused by a combination of excessive cortisol levels overwhelming 11 beta-hydroxysteroid dehydrogenase (the principal enzyme metabolising glucocorticoids) which shows reduced activity under the influence of ACTH and the mineralocorticoid actions of corticosterone and 11-deoxycorticosterone.⁸⁻¹⁰

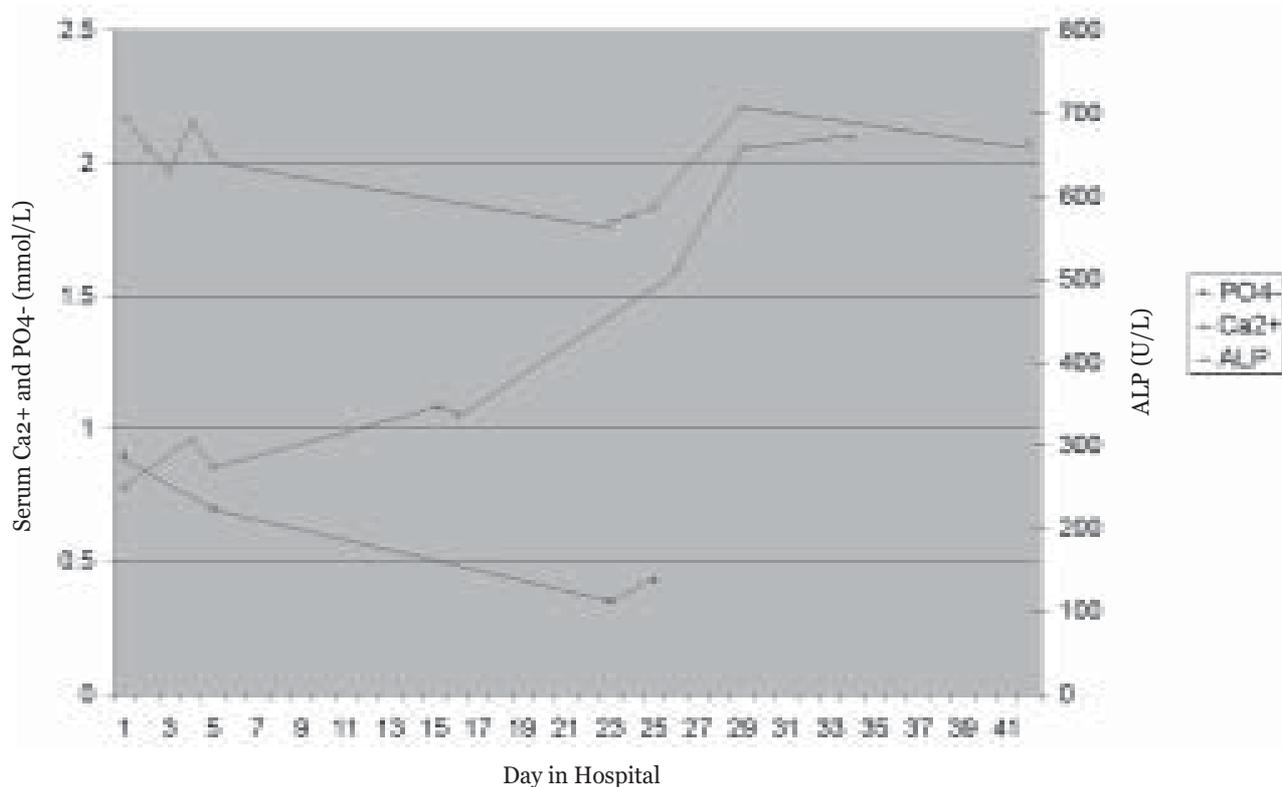
In addition, proximal muscle weakness, weight loss, oedema, impaired glucose tolerance, mental disorders and striking hyperpigmentation are often prominent clinical features. The typical changes in body morphology are usually absent probably due to the rapid onset of the disease and the fast rate of progression. Table 5 shows the frequency of symptoms in ectopic ACTH syndrome associated with small-cell lung cancer.

The occurrence of small-cell lung cancer with ectopic ACTH is associated with a high incidence of infective complications (up to 40 – 50% of patients).^{3,11} Cases of *Pneumocystis carinii* pneumonia, invasive aspergillosis, cryptococcosis, nocardiosis, superficial fungal infections and oral candidiasis have been reported highlighting an increased susceptibility to opportunistic infections unrelated to neutropenia or chemotherapy.¹²⁻¹⁶ In our patient, it is likely that at presentation he was already suffering from diverticulitis with spasm of the bowel wall leading to incomplete obstruction and abdominal distension; this was repeatedly misdiagnosed by different physicians as ascites. Hypercortisolism masked many of the signs and symptoms of inflammation and the infective process progressed to a pericolic abscess and eventual perforation. His post-operative period was also marked by numerous chest infections. The isolation of the low-grade nosocomial pathogen *Alcaligenes xylosoxidans* is unusual in immuno-competent individuals.

High dose dexamethasone suppression test is used to differentiate between ectopic and pituitary-dependent Cushing's syndrome, where 89% of patients with ectopic ACTH secretion fail to suppress.^{8,10,17,18} The altered sensitivity to dexamethasone inhibition may be due to defective action of the glucocorticoid receptor or presence of a glucocorticoid inhibitor within the cells.^{19,20}

Treatment consists of cytotoxic chemotherapy directed against the underlying small-cell lung cancer. However it is usually recommended to start steroid-synthesis blockade before embarking on chemotherapy in an attempt to control hypercortisolism. A number of medications (Table 6) are available but there are various problems associated with their use.²¹⁻²⁴ Ketoconazole is probably the best alternative as it is

Figure 4: Variation of Ca^{2+} , PO_4 and ALP through hospital stay



the least toxic. An alternative is bilateral surgical adrenalectomy, however this is usually reserved for slow-growing tumours or instances when the site of the primary tumour is undetermined.²⁶

Another atypical feature in the case presented was the bone disease. The patient had been complaining of low back pain throughout his second admission. The bone scan did not disclose malignancies but rather thoracic vertebral collapse in keeping with diffuse bone disease. The early demise of the patient precluded further assessment to determine the precise nature of the lesions. One of the possibilities in a hypercortisolaemic state is obviously osteoporosis. The incidence of osteoporosis in small-cell lung cancer does not seem to have been documented in the literature. However anecdotal evidence suggests that incidence is very low probably due to the short natural history of the disease. The other alternative is oncogenic osteomalacia – a paraneoplastic syndrome usually associated with benign head and neck tumours but increasingly reported in cases of malignant carcinomas especially small-cell tumours.^{26,27} Oncogenic osteomalacia is characterised by decreased bone mineralisation secondary to hypophosphataemia in a way similar to X-linked vitamin D resistant rickets. Secretion of phosphatonin, a paraneoplastic factor is thought to inhibit tubular reabsorption of phosphate and conversion of 25- to 1,25-dihydroxyvitamin D.²⁸ Fibroblast growth factor 23 is the strongest candidate as the postulated ‘phosphatonin’.²⁹ The disease is characterised by bone pains, fractures and muscle

weakness. Serum phosphate is very low while calcium and parathyroid hormone level are usually within the normal range. Alkaline phosphatase levels are elevated and 24-hour urinary phosphate excretion is high.³⁰ Figure 4 outlines the calcium, phosphate and alkaline phosphatase assays throughout the patient’s hospital stay.

Ectopic ACTH secretion is associated with a poor prognosis in small-cell lung cancer, due to a combination of factors – tumour burden is usually larger, there is less response to cytotoxic chemotherapy and infectious complications. The median survival reported in the literature from time of diagnosis is approximately 6 months.^{4,11,13}

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