Dual Paraneoplastic Syndromes: Small Cell Lung Carcinoma-related Oncogenic Osteomalacia, and Syndrome of Inappropriate Antidiuretic Hormone Secretion: Report of a Case and Review of the Literature

Ekamol Tantisattamo MD and Roland C.K. Ng MD

Abstract

Acquired isolated renal phosphate wasting associated with a tumor, known as oncogenic osteomalacia or tumor-induced osteomalacia, is a rare paraneoplastic syndrome caused by overproduction of fibroblast growth factor 23. Oncogenic osteomalacia is usually associated with benign mesenchymal tumors. Syndrome of inappropriate antidiuretic hormone secretion (SIADH), on the other hand, is a common paraneoplastic syndrome caused by small cell carcinoma (SCC). Concomitant oncogenic osteomalacia and SIADH associated with SCC is very rare with only 4 other cases reported in the literature. The authors report a case of small cell lung cancer (SCLC)-related renal wasting hypophosphatemia and concurrent SIADH, and review the literature reporting 9 other cases of SCC associated with oncogenic osteomalacia. Almost half of reported cases of renal phosphate wasting associated with SCC concomitantly presented with SIADH. These cases had initial serum phosphorus level lower and survival periods shorter than those without SIADH. This rare combination of a dual paraneoplastic syndrome and low serum phosphorus may be a poor prognostic sign. In addition, both renal phosphate wasting and SIADH usually occur in a short period of time before identification of SCC. Therefore, renal wasting hypophosphatemia with concomitant SIADH/hyponatremia should prompt a search for SCC rather than a benign mesenchymal tumor.

Introduction

Paraneoplastic syndrome is a condition caused by tumors secreting substances which result in a variety of clinical syndromes. Oncogenic osteomalacia, also known as tumor-induced osteomalacia, is a rare metabolic bone syndrome presenting as a paraneoplastic syndrome of isolated renal phosphate wasting, and is usually caused by benign mesenchymal tumors.[1] However, this paraneoplastic syndrome has also been reported to be associated with malignant tumors. As far as the authors are aware, there are 9 previously reported cases of renal hypophosphatemia associated with small cell carcinoma (SCC).[2-9] The authors report one new case of concomitant renal wasting hypophosphatemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with small cell lung cancer (SCLC), and review the literature on the 9 cases of renal hypophosphatemia associated with SCC.

Case Report

A 60-year-old Caucasian man with a history of type 2 diabetes, hypertension, hyperlipidemia, gout, and 80-pack-years smoking presented with chronic hyponatremia starting on March 2007. He refused hospitalization and had persistent hyponatremia ranging from 117 to 130 mEq/L despite fluid restriction for a few months. Two months later, he was admitted with nausea, vomiting, and generalized malaise. His serum sodium was 119 mEq/L. Laboratory workup comfirmed SIADH: euvolemic hypotonic hyponatremia with serum osmolality of 249 mOsm/kg, high urine sodium of 105 mEq/L, high urine osmolality of 680 mOsm/kg, normal thyroid function with TSH of 0.77 μIU/mL (normal range 0.30 – 6.60 μIU/mL), normal adrenal function - morning serum cortisol level of 29.4 μg/dL (normal range 6.0 – 22.4 μg/dL), BUN 4 mg/dL, and serum creatinine 0.6 mg/dL. The patient was treated with fluid restriction, intravenous 3% NaCl, salt tablets, and demeclocycline. His symptoms of hyponatremia improved, but his serum sodium remained low.

In addition, he was found to have persistent hypophosphatemia (serum phosphorus of 1.2 mg/dL). Fractional excretion of phosphorus was 41% (normal < 5%). Other laboratory findings: Serum calcium and albumin were 9 mg/dL and 3.8 g/dL respectively, urine glucose was 2+, alkaline phosphatase was 117 IU/L (normal range 30 – 120 IU/L), 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) was 16 pg/mL (normal range 15 – 60 pg/mL), and total 25-hydroxy vitamin D ($25(OH)D_3$) was 34 ng/mL (normal range 20 – 100 ng/mL). These data support isolated renal phosphorus wasting not due to vitamin D deficiency. He had no family history of renal disease, bone disease, or cancer. He was treated with phosphorus supplementation; however, his serum phosphorus remained low.

Chest X-ray was unremarkable. However, because of a high suspicion for lung cancer, chest computed tomography (CT) scan was done, and showed a 2 cm focal irregular density in the left lung apex and 6.2x4 cm mediastinal mass extending to the left hilum. Bronchoscopy with aspiration and biopsy confirmed SCLC. Abdominal CT scan showed multiple hepatic hypodense masses suspicious for metastases. Bone scan showed no abnormal foci suggestive of metastasis to the skeleton. During the workup for metastases, the patient continued to have hyponatremia (serum sodium 122 - 129), hypophosphatemia (phosphate 1.2 – 1.5), fatigue, and low back pain.

Small cell lung cancer with liver metastases was diagnosed, and chemotherapy with cisplatinum and irinotecan was started. After the first cycle of chemotherapy, his serum sodium was still low, but his serum phosphorus increased to 4.5 mg/dL. Two weeks after chemotherapy, he developed severe diarrhea, pancytopenia, and subsequently septic shock with multi-organ failure requiring vasopressors and increasing ventilator support. He expired one and a half months after the diagnosis of SCLC. Autopsy was not performed.

Review of Literature

The data of the 9 previously reported cases of renal hypophosphatemia-related SCC and of this current case is shown in the Tables 1 and 2. Among these 10 cases reported with oncogenic osteomalacia, five cases had additional paraneoplastic syndrome (4 cases with SIADH, and 1 case with Cushing's syndrome), and one case had two additional paraneoplastic syndromes with SIADH and Cushing's syndrome. SCC occurred at pulmonary sites in 8 cases. The other 2 cases had SCC in extrapulmonary sites: cervical lymph node and urinary bladder. The patients' ages at the time of study ranged between 37 and 72 years. The mean age was 57.8 years. Eight cases were men, and two cases were women.

Table 1. Clinical information of the 9 previously reported cases and of the authors' patient with renal wasting hypophosphatemia associated with SCC

Patient number	Age (years) / Gender / Ethnicity	History of smoking	Symptoms / Duration before the onset of hypophosphatemia	Paraneoplastic syndrome(s)	Site of the primary tumor / Site(s) of the tumor metastasis / Treatment	Bone biopsy	Cause of death / time until death after the onset of hypophosphatemia
2	56 / Female / African-American	NA	Weakness, diffuse body aches and nausea. Temporal wasting/1 month	Fanconi +/- SIADH	Pulmonary / Bone marrow / Chemotherapy	NA	Gram negative septicemia during pancytopenia / 20 months
3	69 / Male	NA	Dysuria, hematuria, urinary frequency, and nocturia / 1 month	Hypophosphatemia	Urinary bladder (Kultschitzky-type cell) / No evidence / Surgery	Not Done	Loss to F/U 15 mo from the onset of hypophosphatemia
4	57 / Male	Yes	Nontraumatic tarsal pain of both feet. Hemoptysis 2 times / 1 month	Phosphate diabetes	Pulmonary / Tarsal and iliac bones / Chemotherapy and radioherapy	Strongly suggestive of osteomalacia	NA / 10 months
5	37 / Male	NA	Mild dysphagia, weight-loss, hemoptyses, and pain affecting the lumbar spine, buttocks, and thighs	Renal phosphate wasting and SIADH	Pulmonary / Not available / Chemotherapy	NA	NA / 15 months
6	57 / Male	NA	Nausea, polyuria, weakness / 1 month (SIADH started first)	Oncogenic osteomalacia and SIADH	Pulmonary / Liver, thoracolumbar spine / Pneumonectomy	Osteomalacia	NA / 3 months
Authors' Patient	60 / Male / Caucasian	80 packs per year	Nausea, vomiting, generalized malaise and weakness / 2 months (SIADH started first)	Renal phosphate wasting and SIADH	Pulmonary / Liver / Chemotherapy	Not Done	Pancytopenia, septic shock with multi-organ failure / 1.5 months
7	72 / Male	1 pack per day, many years	Chest pain and weight-loss / Same	Renal phosphate wasting and SIADH	Pulmonary / No further work-up due to the patient deteriorated rapidly / No	No	NA/ Same period
8	58 / Female	NA	Dysphagia, epgastric pain, weight-loss (1 stone) / 12 months	Oncogenic osteomalacia and Cushing's syndrome	Trachea /Lymph nodes, liver, pancreas, adrenal glands, vertebrae / Esophagectomy	Osteomalacia	NA / 1 month
9	46 / Male	NA	Back pain, cervical adenopathy / Same	Renal phosphate wasting, SIADH and Cushing's syndrome	Extrapulmonary / Bone / Chemotherapy	Not Done	NA / 10 months

NA = Not available

Table 2. Laboratory data of the 9 previously reported cases and of the authors' patient with renal wasting hypophosphatemia associated with SCC

Patient number	Serum phosphorus (mg/dL) (N: 2.5-4.5)		TmP/GFR (mg/dL)	Serum sodium (mEq/L)		Serum cortisol (µg/dL)
	Initial	After tumor treatment		Initial	After tumor treatment	
2	2.2	3.4	NA	132	141	NA
3	1.9	2.7	NA	NA	NA	NA
4	1.36	1.55	0.8	NA	NA	NA
4	1.95	3.75	1.1	NA	NA	NA
5	1.5	NA	Very low	113	No	21 (AM)
6	1.2	Still low	NA	107-	138	17.3
Authors' Patient	1.2	4.5	0.6	117	127	29.4 (AM)
7	0.84	NA	0.4	117	NA	NA
8	0.99	1.08	0.5	143	143	45.38 at 9 am
9	1.2	4.3 -> 1.2-2.8	1.40	107	Corrected and recurrence	35

NA = Not available

The most common presenting symptoms included generalized weakness and musculoskeletal pain. Cervical spinal pain occurred in two cases. Back pain occurred in three cases. Two cases with SCC in the bronchus and trachea had dysphagia. Nine cases had hypophosphatemia before the diagnosis of SCC, but two cases with symptomatic hyponatremia were initially diagnosed with SIADH and were subsequently found to have hypophosphatemia. Two cases developed Cushing's syndrome after hypophosphatemia occurred. Mediastinal lymph node metastases occurred in four cases, and seven cases had distant metastases to brain, visceral pleura, liver, pancreas, adrenal glands, and bone (spine, iliac bone). Three cases had no documented metastasis.

Bone biopsy was reported in four cases. The results from the bone biopsy in two cases showed evidence of osteomalacia, and those from another two cases showed evidence of osteomalacia with increased osteoid. Regarding phosphate excretion, maximum tubular resorption of phosphorus factored for GFR (TmP/GFR) was decreased in six cases (range 0.4 to 1.1 mg/dL), was very low in one case (no value reported), and was not reported in three cases. 1,25 dihydroxycholecalciferol ($1,25(OH)_2D$) was reported in five cases. Two cases had low $1,25(OH)_2D$, and three cases, including this case, had low normal $1,25(OH)_2D$ levels. Fibroblast growth factor (FGF 23), which causes phosphate wasting and is currently thought to be pathogenic in this syndrome, was not reported in any of the cases. In this case, FGF 23 was requested to be sent to a commercial laboratory, but somehow the test was never sent.

Among the ten cases, nine cases received chemotherapy, radiation therapy, and/or surgery. After treatment, serum phosphorus returned to normal in five cases; however, one case had hypophosphatemia recurring after tumor recurrence in conjunction with the presentation of Cushing's syndrome. Serum phosphorus after treatment was not reported in one case. Three of the nine treated cases continued to have persistent hypophosphatemia (1 case after chemotherapy and radiation and two cases after pneumonectomy and esophagectomy). In the one case in which no treatment was given, the patient expired shortly after diagnosis of SCC, and serum phosphorus was not reported before the patient expired.

Among the five cases with concomitant SIADH (one case had both SIADH and Cushing's syndrome), three cases received chemotherapy and/or radiation therapy. Of those three cases, one case had initial resolution of hyponatremia, but the hyponatremia recurred after the tumor recurrence with Cushing's syndrome. Two cases had persistent hyponatremia despite fluid restriction, hypertonic saline, oral sodium tablets, or demeclocycline.

Nine out of ten cases expired. One case reported the cause of death as gram-negative septicemia. This current case had septic shock, pancytopenia, and multi-organ failure after the first cycle of chemotherapy. One case was lost to followup after fourteen months from the diagnosis of SCC of urinary bladder.

Most patients developed the paraneoplastic syndromes, oncogenic osteomalacia and/or SIADH, shortly (not more than 2.5 months for oncogenic osteomalacia and 3.5 months for SIADH) before the diagnosis of SCC. However, a minority developed the paraneoplastic syndromes after diagnosis of SCC (one patient had SIADH three weeks after the SCC diagnosis, and two other patients developed Cushing's syndrome after the diagnosis of SCC). One of these patients presented with hypophosphatemia and oncogenic osteomalacia as long as one year after the SCC diagnosis.

When the one case that was lost to follow-up is excluded, the time until death extended up to 20 months after presenting with hypophosphatemia and the syndrome of oncogenic osteomalacia. Seven out of ten cases had documented distant metastases. Survival did not exceed 20 months after presenting with hypophosphatemia. In four SCC cases presenting with only renal phosphate wasting, initial serum phosphorus ranged between 1.36 and 2.2 mg/dL, and this group had survival ranging between 8 to 20 months. On the other hand, in the four SCC cases presenting with both tumor-induced renal phosphate wasting and SIADH, initial serum phosphorus tended to be more severe between 0.84 and 1.5 mg/dL and initial serum sodium ranged between 107 and 117 mmol/L. Survival in this group was much shorter- only five and four months after presentation with hypophosphatemia and SIADH, respectively. There was no correlation between survival period and normalized serum phosphorus or serum sodium after the treatment of SCC.

In addition to co-existent dual paraneoplastic syndromes of oncogenic osteomalacia and SIADH, there are two cases of SCC associated with oncogenic osteomalacia and Cushing's syndrome.[8,9] One case had a primary tumor in the trachea. Another case had metastatic extrapulmonary SCC, and, interestingly, had triple paraneoplastic syndromes (oncogenic osteomalacia, SIADH, and Cushing's syndrome). Both cases had distant metastases, and developed ectopic corticotropin (adrenocorticotropic hormone [ACTH]) production after renal phosphate wasting developed. They had hypokalemia, high serum and urine cortisol levels, elevated ACTH levels, and lack of suppression with dexamethasone which was consistent with Cushing's syndrome secondary to ectopic ACTH production likely from SCC.

Discussion

Paraneoplastic syndrome is a condition caused by tumors secreting substances which result in a variety of clinical syndromes. SIADH is probably the most common paraneoplastic syndrome in the patient with SCLCs. On the other hand, oncogenic osteomalacia is a rare metabolic bone syndrome presenting as a paraneoplastic syndrome of isolated renal phosphate wasting, and is usually caused by benign mesenchymal tumors.[1] Oncogenic osteomalacia occurs with a malignant tumor in only 10% of cases, and thus the dual combination with SIADH is extremely rare. However, from this review, five out of 10 cases of renal phosphate wasting associated with SCC also presented with SIADH.

Tumor-associated SIADH results from inappropriate secretion of antidiuretic hormone (ADH), also known as arginine vasopressin (AVP), from some tumors. SCLCs, which are neuroendocrine tumors, can express the arginine-vasopressin-neurophysin II (AVP-NP II) gene increasing AVP production.[10] AVP controls AVP-regulated water channels called aquaporin-2,[11] located on the luminal membrane of principal cells of cortical and medullary collecting tubules, and causes water reabsorption into the cell and then interstitium.[1] SCLCs account for 75% of cases of SIADH caused by tumors.[12]

Oncogenic osteomalacia, also known as tumor-induced osteomalacia, is a rare paraneoplastic syndrome frequently associated with mesenchymal tumors of mixed connective tissue in the bone or soft tissue.[13] The most common sites of tumors causing oncogenic osteomalacia are osseous (55% long bone, 30% head and neck, and 20% upper extremities), soft tissue including skin (66% in the lower

extremities).[13] However, 10% of cases are due to malignant tumors and 5% are from tumors from multiple sites.[14] Reported malignant tumors associated with oncogenic osteomalacia include prostatic cancer,[15] multiple myeloma,[16] small cell carcinoma of the lungs,[2, 4-6, 9] the urinary bladder,[3] and extrapulmonary lymph nodes.[8] These tumors highly express the FGF23 gene producing FGF23 which has phosphaturic and inhibitory 1-α-hydroxylase activities. An increase in levels of FGF23 causes decreased expression of sodium-phosphorus cotransporters in the proximal tubules of the kidney which then results in decreased renal phosphate reabsorption. The inhibitory effect of FGF23 on 1-α-hydroxylase also leads to decreased production of $1,25(OH)_2D$ which then causes a decrease in intestinal phosphorus absorption which potentiates the hypophosphatemia. Low levels of $1,25(OH)_2D$ also stimulate parathyroid hormone (PTH) secretion, which contributes to decreased renal phosphorus reabsorption.[1] Mobilization of phosphorus from skeleton over a long period of time then results in osteomalacia. Even though markedly elevated FGF23 is pathogenic in oncogenic osteomalacia and can be a marker of oncogenic osteomalacia.[17, 18] Elevated levels of FGF23 can also be found in other diseases such as X–linked hypophosphatemia (XHP) and chronic kidney disease.

Renal phosphate wasting can be divided into congenital and acquired conditions. Two rare inherited diseases causing isolated renal phosphate wasting are X–linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets (ADHR).[19,20] The patients with these two disorders present in childhood and have a familial history.

The most common cause of acquired renal phosphate wasting is primary hyperparathyroidism.[20] Oncogenic osteomalacia is a rare cause of acquired renal phosphate wasting, which mostly occurs in adults with an average age of 33 years (range between age 7 to 73).[13] The onset of oncogenic osteomalacia may precede the diagnosis of tumor with a range between 3 months to 17 years.[14] Clinical manifestations of oncogenic osteomalacia include biochemical findings and bone abnormalities. Chronic hypophosphatemia causes a deficiency in osteoid mineralization and osteomalacia. In addition to hypophosphatemia, other biochemical features include renal phosphate wasting, low $1,25(OH)_2D$ levels, increased alkaline phosphatase, and normal calcium, parathyroid hormone (PTH), calcitonin, and $25(OH)D_3$ levels.[13] Patients with oncogenic osteomalacia often present with the symptoms of osteomalacia; bone pain, muscle pain, or recurrent fractures.[1] Stress fractures can occur as pseudofractures, or Looser-Milkman lines, which are the typical radiological findings of oncogenic osteomalacia.[13]

In the authors' patient, hypophosphatemia was found at the time of diagnosis of SCLC. He had the typical biochemical features including hypophosphatemia from documented renal phosphate wasting, low normal $1,25(OH)_2D$, high normal alkaline phosphatase, and normal calcium and $25(OH)D_3$ levels. However, there were no radiological findings of osteomalacia. He had hypophosphatemia 1.5 months before death, so the duration of hypophosphatemia may have been too short to develop radiographic changes.

The most definitive diagnostic criterion of oncogenic osteomalacia is reversal of biochemical abnormalities following tumor resection. However, most of the time, oncogenic osteomalacia results from slow growing mesenchymal tumors some of which are very small and may not be detected from screening imaging. As a consequence, localization of the tumor is difficult.[21] Ito N et al, reported the usefulness of systemic venous sampling of FGF 23 from specific large venous vessels (eg, subclavian, internal jugular, brachiocephalic, superior vena cava, inferior vena cava, common iliac, external iliac, internal iliac, and femoral veins) in order to guide and select the possible location of tumor where the imaging (CT scan and/or MRI) should be directed. They found that venous sampling with the highest FGF 23 level suggested the location of responsible tumors in 8 out of 10 cases.[22]

Systemic venous sampling of FGF 23 is not a general test, but it can be safely performed with interventional radiology. However, it may not always identify the responsible tumor which is distal to the vein having the highest FGF 23 level. The reliability of the test depends on the technique, how selectively blood samples are collected, the location of the tumor, and the rate of FGF 23 secretion from the responsible tumor.[23] In addition to identifying the location of tumor, FGF 23 can be used to monitor response to treatment since the level will decrease rapidly after tumor resection.[24]

In the authors' patient, because SCLC is an aggressive and generally incurable malignant tumor, it is difficult to prove the causal relationship between SCLC and renal phosphate wasting by complete removal of SCLC. However, the clinical features of acquired renal phosphate wasting in the authors' patient are compatible with oncogenic osteomalacia, and his serum phosphorus normalized after the first cycle of chemotherapy, suggesting that the renal phosphate wasting in the authors' patient was likely due to oncogenic osteomalacia associated with SCLC.

The appearance of SIADH in SCLC does not correlate with chemotherapy or survival.[25] On the other hand, from Table 1, seven out of 10 cases of SCC with renal phosphate wasting had distant metastases, and survival in those also presenting with SIADH was shorter than the group with only renal phosphate wasting. The average initial serum phosphorus level was lower in the patients with combined SIADH. In SCC, renal phosphate wasting associated with concomitant SIADH, as well as the lower initial serum phosphorus, may be a poor prognostic sign or a marker of terminal SCC. Therefore, a high index of suspicion should be raised in patients with both acquired renal phosphate wasting and SIADH and should prompt an investigation for underlying malignancy, especially SCLC, rather than a benign mesenchymal tumor as in most cases of oncogenic osteomalacia.

Oncogenic osteomalacia and Cushing's syndrome were co-existent in two patients who expired shortly after Cushing's syndrome was diagnosed. The short survival periods in these patients may be due to a poor prognosis of SCLC especially when it is associated with ectopic ACTH production[26] and low initial serum phosphorus.

Symptoms of SIADH depend on the severity of hyponatremia and especially the rate of decrease in serum sodium. Many patients with SIADH are relatively asymptomatic because the hyponatremia developed gradually. Patients with oncogenic osteomalacia may present with pain or musculoskeletal problems, or an abnormal bone x-ray. Treatment of oncogenic osteomalacia usually consists of surgically removing a benign mesenchymal tumor, which results in complete resolution of signs and symptoms. However, if the tumor is not totally removed or malignant tumors are not completely treated, symptoms and signs of hypophosphatemic osteomalacia will remain. In such a case, symptomatic treatment with phosphorus

replacement and calcitriol can be used to alleviate the symptoms of hypophosphatemia such as pain and weakness.

Conclusion

Paraneoplastic SIADH is commonly associated with SCLC, but oncogenic osteomalacia is rarely found in patients with SCLC. Dual paraneoplastic syndromes, oncogenic osteomalacia and SIADH, are even more uncommon.

In almost half of the nine reported cases of oncogenic osteomalacia associated with SCC, the patients concomitantly presented with SIADH. These patients had lower initial serum phosphorus levels and shorter survival periods than those without SIADH. The presence of dual paraneoplastic syndromes with a very low serum phosphorus may be a poor prognostic sign. In addition, renal phosphate wasting and hyponatremia usually appear in a short period of time before identification of SCC. Therefore, an expedited work-up for a malignant lung tumor, rather than a benign mesenchymal tumor, should be pursued in the adult who presents with both oncogenic osteomalacia and SIADH.

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Authors' Affiliation:
- Department of Medicine, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI 96813

Correspondence to:
Ekamol Tantisattamo MD; Department of Medicine, John A. Burns School of Medicine, University of Hawai'i; 1356 Lusitana Street, UH Tower 7th floor, Honolulu, HI 96813; Ph: (808) 586-2910, Fax: (808) 586-7486; Email: ekamol@hawaii.edu

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