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Small Cell Carcinoma of the Prostate and the Syndrome of Inappropriate Antidiuretic Hormone: A Rare Entity and Presentation

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The syndrome of inappropriate antidiuretic hormone may be associated with numerous clinical conditions including malignancy, benign pulmonary and neurologic disease, and as a drug side effect. SIADH caused by malignancy most commonly occurs in small cell carcinoma of the lung; prostate cancer is an extremely rare cause of this syndrome. We report an exceptional case of SIADH caused by small cell carcinoma of the prostate. This case emphasizes the propensity of small cell cancers of any primary site to cause paraneoplastic phenomena and demonstrates the serendipitous usefulness of positron emission tomography scanning as a diagnostic tool rather than a staging investigation.

PATIENT DESCRIPTION

A 68 year old man was admitted as an emergency with a short history of general malaise and muscle cramps, and after his general practitioner had found severe hyponatremia. He was usually well and denied any respiratory, urological or neurological symptoms, or weight loss. He had no previous history of tuberculosis or any other past history of note other than nasal polyps. He drank no more than 10 units of alcohol per week but had a 30 pack-year history of smoking. His only medication was mometasone nasal spray. He had spent many years working in a foundry and subsequently the fireplace industry.

On admission, the patient was alert and well oriented; he was euvolemic and there were no signs of pitting edema. Laboratory investigations showed serum sodium 115 mmol/L (normal range 135–144 mmol/L), potassium 4.4 mmol/L (normal range 3.5–5.3), urea 5.0 mmol/L (normal range 2.1–7.6) and creatinine 89 μmol/L (normal range 56–127). His liver function, calcium and full blood count were normal. Serum osmolarity was 248 mOsm/kg (normal range 300–900) and urine osmolarity 656 mOsm/kg (normal range 300–900). Thyroid function and a short synacthen test were normal.

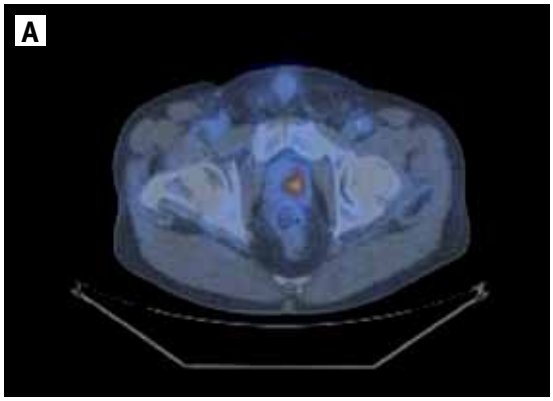
His hyponatremia was compatible with SIADH, and given his smoking history occult lung cancer was strongly suspected. His chest radiograph showed bilateral hilar adenopathy with egg shell calcification. A computed tomographic scan of his chest and abdomen confirmed the findings on the chest X-ray, showing enlarged and partially calcified mediastinal and hilar lymph nodes in keeping with previous exposure to silicates. There was no obvious intrapulmonary mass or intra-abdominal abnormality. Flexible fiberoptic bronchoscopy showed a slightly edematous carina and mucosal cobblestoning of the left upper lobe bronchus. Bronchial brushings and biopsies showed no evidence of malignancy or granulomas.

There remained a high likelihood of small cell carcinoma of the lung, perhaps arising in one of the hilar nodes, and a fludeoxyglucose positron emission tomography scan was arranged prior to possible mediastinal node biopsy. However, his PET scan [Figure A] showed increased uptake (max SUV 9.2) in the left lobe of the prostate with a soft nodule in the seminal vesicle and the left iliac lymph node. There was lesser uptake in the aortopulmonary lymph nodes (max SUV 4.6) and both axillae (max SUV 3.8), compatible with malignancy or granulomatous inflammation. There was no evidence of abnormal uptake in the lungs.

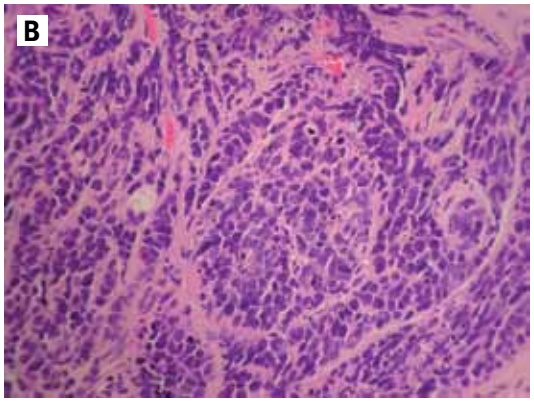
A transrectal ultrasound-guided prostate biopsy was subsequently performed. This revealed small cell carcinoma [Figure B], which explained his severe SIADH. Immunohistochemical studies were negative for prostate-specific antigen [Figure C] and positive for thyroid transcription factor-1 [Figure D]. His repeated serum PSA was normal: 1.0 μg/L (normal range 0–4 μg/L). His small cell carcinoma of the prostate was treated with carboplatin and etoposide, but his hyponatremia did not improve following chemotherapy. He was fluid restricted but did not tolerate this well and was therefore started on demeclocycline 300 mg twice daily. The response was good and his serum sodium returned to normal (139 mmol/L). Following chemotherapy, the tumor regressed. Unfortunately, the SCCP relapsed 14 months later with multiple metastases to his liver and spine, and he died a month later.

SIADH = syndrome of inappropriate antidiuretic hormone

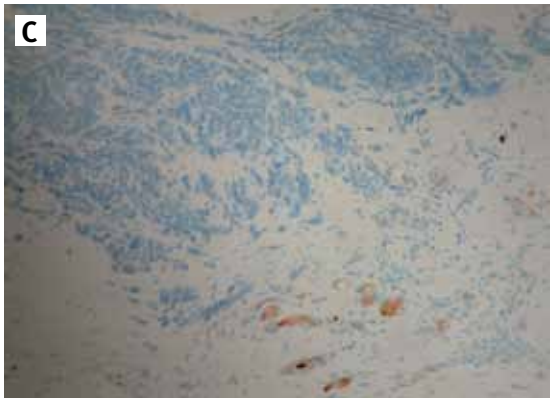
PET = positron emission tomography
PSA = prostate-specific antigen
SCCP = small cell carcinoma of the prostate



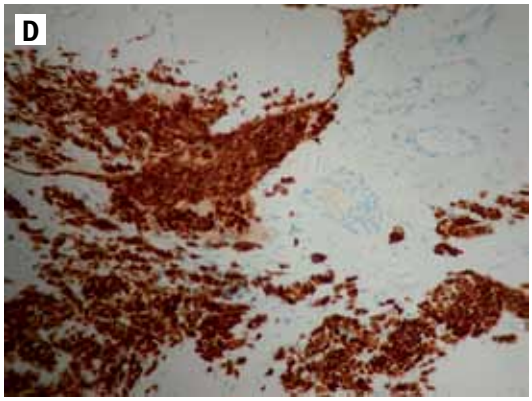
[A] Positron emission tomography scan showing increased uptake in the left lobe of the prostate



[B] Histologic findings on the prostate biopsy showing small cell carcinoma



[C] Immunohistochemistry for PSA showing no immunoreactivity



[D] Tumor cells showing immunoreactivity for thyroid transcription factor-1

COMMENT

SIADH is one of the commonest causes of hyponatremia in hospitalized patients. The diagnostic criteria for SIADH are based on findings of serum hyponatremia with inappropriately high urinary sodium concentration in a euvolemic individual with unimpaired renal and endocrine function [1]. Our patient showed findings consistent with SIADH. Metastatic small cell carcinoma of the prostate was the likely cause of the SIADH. However, pulmonary diseases such as pneumonia, lung abscess, tuberculosis and small cell lung cancer [1] are known to cause SIADH. Although there was evidence of previous silicate exposure as judged by calcified hilar nodes, there was no evidence to suggest acute active silicotic lung disease with lymphadenopathy, nor is it recognized to cause SIADH.

SIADH caused by malignancy most commonly occurs with small cell carcinoma of the lung, with a reported incidence of 11%. Prostate cancer can present as SIADH but this is rare. Most cases of SIADH caused by prostatic carcinoma are adenocarcinomas, the most common histologic subtype of prostate cancer. Primary SCCP is extremely rare and accounts for only 1–2% of all prostatic malignancies. Primary SCCP presenting as SIADH is even rarer, with only three previous published case reports [2-4]. The exact mechanism of SIADH from SCCP is unclear. However, high levels of ADH have been detected immunohistochemically in the tumor tissue of SCCP, and it is presumed that there is an overproduction of ADH from the genetically abnormal prostate carcinoma cells [3].

The histologic origin of SCCP is controversial; however, the tumor may arise from either a malignant transformation of the normal neuroendocrine cell population or a multipotential stem cell of the prostatic epithelium. The prostatic neuroendocrine cells have regulatory functions and produce a variety of secretory products and peptides such as chromogranin A, neuron-specific enolase, synaptophysin, thyroid transcription factor-1, parathyroid-related protein, and carcinoembryonic antigen. These neuroendocrine makers are used in the immunohistochemical confirmation of the diagnosis of SCCP, in addition to the lack of PSA and androgen receptor positivity [3,5] .

Early diagnosis of SCCP is often difficult because it has a predilection to metastasise early to visceral organs and regionally to pelvic lymph nodes, rectum and bladder without a concordant rise in PSA [5]. As in our case, metastatic disease was

evident on the PET scan and his repeated PSA was consistently normal. At the time of diagnosis, most patients with SCCP are symptomatic with constitutional and obstructive symptoms, followed by paraneoplastic syndromes, hematochezia and hematuria. In the three previous cases of SCCP presenting with SIADH, the patients had symptoms of anorexia, rectal bleeding with subsequent abnormal prostate examination, and painless hematuria [2-4] which suggested the possible diagnosis of prostate cancer. Our case is unique in that there were no presenting symptoms to help localize the primary site of a malignancy, and the PET scan was crucial in alerting us to the diagnosis of prostate cancer.

There is no standardized treatment for SCCP due to its rarity, and it is generally managed by chemotherapy regimens similar to those for small cell carcinoma of the lung. The results are generally unfavorable and prognosis is poor with a median survival of 7 months [5].

The initial treatment of the hyponatremia in SIADH is fluid restriction, and in patients where fluid restriction is difficult demeclocylicine can be used. In small cell tumors of the lung the hyponatremia may improve during cytotoxic combination chemotherapy of the primary tumor, but unfortunately that was not the case here. A recently introduced oral non-peptide vasopressin receptor antagonist, tolvaptan, may be an alternative option in the treatment of SIADH if all other measures fail. Hypertonic saline may be necessary as emergency treatment in those with neurologic symptoms where correction of the metabolic defect is urgent [1].

In summary, this case demonstrates the propensity of small cell tumors to cause similar paraneoplastic syndromes regardless of the site of origin. Early diagnosis and management of primary SCCP is important but challenging because it metastasizes early without a concordant rise in PSA. While PET scan imaging is well established for tumor staging, it is also a useful investigation when malignancy is strongly suspected but where the primary site is unknown.

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