Bratisl Lek Listy 2008; 109 (8)
362 – 363

CASE REPORT

Paraneoplastic Cushing's syndrome as the first sign of progression of prostate cancer

Rajec J[1], Mego M[1], Sycova-Mila Z[2], Obertova J[2], Brozmanova K[2], Mardiak J[1]

Department of Medical Oncology School of Medicine, Comenius University, Bratislava, Slovakia.
jan.rajec@fmed.uniba.sk

Abstract: Cushing's syndrome accompanying the small cell de-differentiation of the prostatic adenocarcinoma is a relatively rare clinical entity, associated with poor overall prognosis. Despite several treatment options available, there is still no effective standard therapy for this clinical condition. Herein, we report two patients with prostate cancer presenting with clinical and laboratory features of Cushing's syndrome as the first sign of disease progression *(Ref. 4)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: prostate cancer, paraneoplastic Cushing's syndrome, disease progression.

The paraneoplastic Cushing's syndrome caused by adrenocorticotropic hormone (ACTH) or corticotrophin-releasing factor (CRF) production by non-endocrine tumours is mostly associated with the small cell lung cancer (SCLC). However, the small cell de-differentiation of the prostatic adenocarcinoma accompanied by Cushing's syndrome is relatively rare. The so far reported several cases in the literature documented very aggressive behaviour of this hormonally insensitive tumour, with poor overall prognosis. The presence of this syndrome is considered an independent negative prognostic factor with high rate of chemotherapy complications and poor overall survival (1).

It is often problematic to make an early diagnosis of this syndrome. The typical clinical manifestations include accelerated weight gain, centripetal fat distribution, muscle weakness, secondary hypertension and generalized oedemas. Laboratory findings such as hypokalaemic alkalosis, hypernatriemia, high levels of serum cortisol, ACTH and increased 24-h urinary cortisol levels are usually sufficient for making the diagnosis (2). Hypertension is another sign of this syndrome.

We based our diagnosis on typical clinical and biochemical findings. The bone marrow examination confirmed bone marrow infiltration by poorly differentiated small cell carcinoma in both cases. As for the therapy, the management of patients affected by this rare complication remains difficult. Tumour shrinkage of >90 % often needed to normalise the paraneoplastic endocrine status is not commonly achieved (3). Paradoxically, in our cases paraneoplastic syndrome occured despite tumor response to chemotherapy. We suppose that this was due to the selection of chemotherapy resistant clone causing hypercorticism. Another possibility is that chemotherapy lead to differentiation of cancer cells to ACTH producing cells.

Despite testing several potentially effective drugs in the medical management of ectopic Cushing's syndrome (e.g. octreotide, aminoglutethimide, ketoconazole, metyrapone or mitotane), none of them has been accepted as standard therapy and their common usage is still controversial (4). The rapid onset and aggresive cause of the disease in both our cases would probably not allow to achieve full effect of these drugs.

Herein, we report two cases of prostate adenocarcinoma with dedifferentiation to small cell prostate cancer, with new onset of paraneoplastic Cushing's syndrome despite previous tumor response to chemotherapy.

CASE REPORT 1

51 year old man presented to his urologist with voiding problems and low back pain. Digital rectal examination revealed enlarged prostate. Biopsy obtained by transurethral resection revealed poorly differentiated Gleason 9 adenocarcinoma with small/neuroendocrine component. Bone scan showed numerous bone metastases. He was treated with combined androgen blockade comprising a gonadotropin releasing hormone analog of 22.5 mg every 3 months and antiandrogen flutamid of 250 mg orally three times daily. Additionally, 4 mg of zoledronic acid were administered every 4 weeks.

Twenty months later, he experienced increased frequency, gross hematuria and pain under right epigatrium. PSA was within normal range, however neuron-specific enolase (NSE) was 1350 ng/mL. He underwent repeated transurethral resection with histology of small cell prostate carcinoma. Laboratory tests showed severe thrombocytopenia, anemia and elevated liver function tests (LFTs). CT scan revealed multiple liver metastases and enlarged

[1]Department of Medical Oncology School of Medicine, Comenius University, Bratislava, [2]National Cancer Institute, Bratislava, Slovakia

Address for correspondence: J. Rajec, Department of Medical Oncology, Faculty of Medicine, Comenius University, Klenova 1, SK-833 10 Bratislava, Slovakia.
Phone: +421.2.59357, Fax: +421.2.59357

retroperitoneal lymphnodes. Bone marrow examination showed massive infiltration by small cell carcinoma. Subsequently, he was treated with 3 cycles of etoposide 120 mg/m^2 day 1 to 3 and cisplatin 70 mg/m^2 day 1 every 3 weeks, with regression of liver metastases, improvement of anemia, and normalisation of thrombocytopenia. NSE decreased to 129 ng/mL. Before starting the fourth cycle, he noted weakness of legs and fatique and mental status changes. Laboratory tests revealed marked hypernatremia, hypokalemia, hyperglycemia, hypokalemic alkalosis. These findings, with new onset of mild hypertension suggest paraneoplastic Cushing's syndrome, which was confirmed by elevated plasma cortisol level, failed to decrease following either low or high-dose dexamethazone administration. Ketokonazol treatment was started, however without effect on hypercorticism. However, CT scan showed regression of liver metastases and retroperitoneal lymphnodes. Additional finding on CT scan was pneumoperitoneum due to perforated sigmoid colon. Patient underwent urgent surgery, however, his status deteriorated rapidly and 2 weeks after the surgery, he died.

CASE REPORT 2

Our second clinical case reports a 70-years old patient with prostatic adenocarcinoma Gleason 7, grade 2 with axial bone metastases treated for 3 years by hormonal therapy (gonadotropin releasing hormone analog) in the urological clinic. Additionally, the patient received 4mg of zoledronic acid every 4 weeks for 2 years.

Due to the progression of bone metastases accompanied by bone pain, and elevated PSA 32 ng/mL. he was reffered to our department and was treated with docetaxel 75mg/m^2 every 3 weeks and prednison 5 mg bid. He received 5 cycles of chemotherapy with normalization of PSA and disapearance of bone pain. Six months later, he was admitted in our ward due to progressive fatigue, dyspnoea and hematuria. The performed laboratory tests revealed severe anemia, thrombocytopenia and renal impairment. Serum PSA was within normal ranges. The kidney ultrasound examination showed massive prostatic tumor infiltrating the urinary bladder, causing uretheric obstruction. CT scan revealed multiple liver metastases. The right side nephrostomy was performed with subsequent improvement of kidney function tests. The elevation of the NSE together with persistent PSA negativity supported our assumption of the small cell neuroendocrine de-differentiation of the former prostatic adenocarcinoma. Bone marrow examination showed hypocellular bone marrow infiltrated by poorly differentiated neuroendocrine carcinoma.

Based on these findings, he was treated with etoposide 120 mg/m^2 day 1–3 and carboplatin area under curve (AUC) = 5, every 3 weeks. He achieved quick clinical and marker response, assessed by bleeding cessation, significant NSE decrease (from 436 to 36 ng/ml) and improvement of anemia and thrombocytopenia. The second chemotherapy cycle was initiated with one week delay due to diarrhea grade 2. However, the second treatment cycle was complicated by prolonged thrombocytopenia and leukopenia grade 4 beginning early on day 5, despite the leukocyte growth factor support. Morever, laboratory tests performed on day 13 of the second cycle showed severe metabolic dysbalance: hypernatremia, hypokalemia, hyperglycemia and hypokalemic alkalosis. The suspicion of paraneoplastic hypercorticism was confirmed by highly elevated cortisol levels in the morning blood sample (1340 nmol/l). The corresponding clinical manifestations included treatment refractory hypertension, peripheral oedemas and mental status deterioration. Brain CT scan was normal. Liver function tests and elevated bilirubin reflected disease progression in the liver confirmed by ultrasound examination. Patient status deteriorated rapidly and the patient died within 2 weeks of onset of signs of hypercorticism.

Conclusion

The paraneoplastic Cushing's syndrome accompanying small cell de-differentiation of the prostatic adenocarcinoma described in our two case reports is a rare clinical entity associated with poor overall prognosis. The aggresive biological behaviour with high metastatic potential and transient chemotherapy response as main typical features of this malignancy were also documented in our two patients. Currently, there are no effective therapeutical regimens available. Thus, further research is warranted to achieve better treatment results.

References

1. Nimalasena S, Freeman A, Harland S. Paraneoplastic Cushing's syndrome in prostate cancer: a difficult management problem. BJU International 2007; 101: 424—427.

2. Torpy DJ, Mullen N, Ilias I, Nieman LK. Association of hypertension and hypokalaemia with Cushing's syndrome caused by ectopic ACTH secretion. Ann NY Acad Sci 2002; 970: 134—144.

3. Hsu CHK, Cheng CHJ, Chen KCH, Chiang HS, Chu JS. Prostatic Pure Small Cell Carcinoma v.s. Mixed-Type Small Cell Carcinoma: Analysis of Two Cases. JTUA 2005; 16: 115—119.

4. Trotz CH. Prostate cancer with a normal PSA: Small Cell Carcinoma of the Prostate — Rare Entity. J Amer Board Family Pract 2003; 16: 343—344.

Received May 19, 2008.
Accepted June 15, 2008.