

# Paraneoplastic syndromes (PNS) in urological malignancies

## Abstract

Malignancies of the genitourinary tract are currently diagnosed more frequently than ever in the past. While for some of them, like prostate cancer, available treatment options are likely to lead the majority of patients to cure from the disease, for others, like renal cancer, advanced disease will eventually lead to death within months. This coupled with the fact that the average life expectancy in the Western World is increasing will result in a vast patient population with either advanced, non-curable disease or cancer survivors with problems related to the received therapeutic surgical or medical interventions. The care of patients with advanced urologic malignancies requires a multi-disciplinary effort from physicians of many specialties under the guiding role of the treating urologist. We will discuss a less recognized cause of suffering for patients with advanced malignancies, the issue of paraneoplastic phenomena and their management.

Volume 1 Issue 1 - 2014

Petros Sountoulides,<sup>1</sup> Ioannis Mykoniatis,<sup>1</sup>  
Vasilios Nikolaou,<sup>1</sup> Athanasios Bantis<sup>2</sup>

<sup>1</sup>Urology Department, General Hospital of Veria, Greece<sup>2</sup>Urology Department, University Hospital of Alexandroupolis, Greece

**Correspondence:** Petros Sountoulides, Urology Department, General Hospital of Veria, Greece, Tel +302310452560, Email [sountp@hotmail.com](mailto:sountp@hotmail.com)

**Received:** September 29, 2014 | **Published:** September 30, 2014

**Abbreviations:** PNS, paraneoplastic syndromes; PTHrP, parathormone-releasing peptide; RCC, renal cell carcinoma; EDTA, ethylene diamine tetra acetic acid; G-CSF, granulocyte colony-stimulating factor; IL-6, interleukin-6; CACS, cancer anorexia-cachexia syndrome; VEGF, vascular endothelial growth factor; EPO, erythropoietin; HIF, hypoxia-inducible factor

## Introduction

Paraneoplastic syndromes (PNSs) are defined as a plethora of symptoms and clinical signs occurring in cancer patients and involving systemic effects taking place remotely from the tumor. These symptoms are not related either to its local repercussion or distant spread and are not caused by infection, nutritional deficiency or treatment.<sup>1</sup> Recognition of a PNS is clinically important as it can lead to the diagnosis of a previously undetected neoplasm or more often can be used as a surrogate “tumor marker” of disease progression or remission as it follows the clinical course of the causative malignancy. The most prominent PNSs associated with urological malignancies and especially renal cancer will be discussed in more detail.

## Paraneoplastic hypercalcemia

Hypercalcemia of malignancy (HM) is the most common endocrine PNS and accounts for approximately 30% of all Hypercalcemia cases. Parathormone-releasing peptide (PTHrP) production leading to HM is a well-described paraneoplastic phenomenon which may be seen in as many as 20% of patients with cancer, usually small cell carcinomas of breast, lung, and genitourinary tract.<sup>2</sup>

HM is the most common PNS among patients with renal cell carcinoma (RCC). Of those with Hypercalcemia and RCC, approximately 75% have high-stage lesions and 50% harbor bone metastasis, although neither the presence nor the degree of Hypercalcemia have been shown to significantly correlate with tumor grade or survival.<sup>3,4</sup>

The clinical picture of HM can be very polymorphic with some patients showing nonspecific symptoms such as asthenia, headache, lack of appetite, nausea, vomiting, constipation, somnolence,

polyuria-polydipsia (due to nephrogenic diabetes insipidus), and others exhibiting a more severe and specific clinical presentation such as acute confusional or lethargic state or even coma associated with very high serum calcium ( $\text{Ca}^{++} > 12\text{mg/dl}$ ). When calcemia exceeds 18mg/dl, shock and death occur.<sup>1</sup> The usual laboratory pattern is that of an elevated total and ionized calcium in the absence of other causes (bone metastases), low PTH values (PTH may be over the lowest value of the reference interval), and high levels of phosphates. Measurement of PTHrP can be helpful in the diagnosis of an otherwise unexplained Hypercalcemia.

HM cases do not usually require pharmacologic treatment since physiological homeostatic mechanisms and volume repletion either orally or i.v can usually maintain calcium levels under safety limits. If necessary, drugs which inhibit osteoclasts and interrupt the vicious cycle of bone resorption (bisphosphonates, denosumab) or favor calcium fixation in the bone (calcitonin) can be employed. The addition of corticosteroids or diuretics to hydration and i.v bisphosphonates has not been established, although some patients will require diuresis if they develop clinical volume overload.<sup>5</sup>

In refractory cases, calcitonin, EDTA (ethylene diamine tetra acetic acid) or plicamycin (mithramycin), an agent that decreases serum calcium concentrations by inhibiting RNA synthesis in osteoclasts, may be employed although the use of these agents is limited by difficulties in administration and side-effects. (e.g. several daily s.c. injections for calcitonin and prolonged myelo suppression from mithramycin).<sup>5</sup> For the extreme case of very high levels of calcemia the use of hemodialysis may become necessary.

## Paraneoplastic leukocytosis

Paraneoplastic leukocytosis is common in cancers and has been described for RCC and urothelial carcinomas of the bladder and pelvis.<sup>6,7</sup> It has been attributed to tumor production of granulocyte colony-stimulating factor (G-CSF) which in turn promotes the development of mature neutrophils from hematopoietic progenitor cells.<sup>1</sup> The diagnostic evidence includes marked leukocytosis with predominant mature neutrophils, elevated serum G-CSF, positive

immune histo chemical staining of tumor cells with anti-G-CSF antibody, leukocytosis and elevated serum G-CSF that reverses following tumor excision.

### Constitutional symptoms

Constitutional symptoms are usually, but not exclusively, associated with the presence of RCC since it is estimated that 10–40% of patients with RCC will develop a PNS.<sup>1</sup> Most PNS associated with localized or at least surgically resectable RCC are definitively treated with nephrectomy. Pyrexia, anemia, weight loss, and fatigue can be the first symptoms of RCC in up to one third of cases. Unexplained fever is found in 20–30% of RCC and is the sole presenting complaint in approximately 2% of patients. These and other constitutional symptoms in advanced RCC are thought to be mediated by cytokines such as TNF- $\beta$ , IL-6, IL-1, interferon's and prostaglandins. Anemia can occur for various reasons and is observed in about 20% of RCC patients. Poor nutritional status and the presence of a chronic disease are two main reasons for the anemia that, however, has been also related to tumor production of Interleukin-6 (IL-6) and iron-binding proteins, such as ferritin and lactoferrin.<sup>8,9</sup> It is important to clinically evaluate the patient for signs of microscopic or macroscopic haematuria or alternative sites of bleeding, as well as potential iron, vitamin B12 or folate deficiency, before attributing their anemia to paraneoplastic syndromes. The management of anemia with administration of erythropoietin results in an increase of 1–2 g/dL in hemoglobin over a 6–12 weeks' course. For patients in need for more rapid increase in hemoglobin treating physicians should consider red-cell transfusion.<sup>5</sup>

One of the commonest paraneoplastic syndromes associated with RCC is cancer anorexia-cachexia syndrome (CACS), which can manifest as anorexia or dysgeusia (altered sensation of taste and foul-smelling breath), malaise, night sweats, involuntary weight loss and poor performance. In a recent study cachexia as well as polycythemia and hypercalcemia have been correlated to vascular endothelial growth factor (VEGF) expression.<sup>4</sup> CACS should be suspected if a patient has involuntary weight loss of more than 5% of pre-illness weight over a 2- to 6-month period. A recent study showed that among patients with at least one PNS, cachexia, the occurrence of a varicocele and pyrexia were related to advanced RCC stage.<sup>4</sup> Once non-neoplastic causes of constitutional symptoms in patients with RCC have been ruled out, nephrectomy is the most effective treatment. Palliative treatment regimens consist of either a low-dose corticosteroid (hydrocortisone, 20mg twice a day), or progesterone, 800mg/d, however responses are usually transient. If symptoms persist after nephrectomy, metastatic disease is usually present and prognosis is dismal.<sup>10</sup>

### Polycythemia and abnormal erythropoietin production

Paraneoplastic polycythemia by cancerous overproduction of erythropoietin (EPO) is generally rare, but not infrequently seen in patients with renal cell carcinoma (RCC) where it involves 1–8% of patients.<sup>1</sup> Elevated red blood cell concentrations are thought to be mediated by erythropoietin (EPO), a glycoprotein produced by peritubular renal interstitial cells that promote red blood cell production in the bone marrow. The majority of clear cell RCC displays a strong activation of the Hypoxia-inducible Factor (HIF), the transcription factor regulating EPO. The frequency of EPO gene expression in RCC is therefore much higher than the prevalence of clinical polycythemia.<sup>11</sup>

Excessive EPO production occurs in the tumor cells themselves,

although perineoplastic cells may also contribute, secondary to local tumor compression and resultant tissue hypoxia.<sup>12</sup> In cases of localized disease, EPO levels normalize following nephrectomy, whereas they remain elevated or rise again in those with metastatic disease or late tumor recurrence.<sup>13</sup>

### Stauffer's syndrome

Non-metastatic hepatic dysfunction in patients suffering from renal cell carcinoma, known as Stauffer's syndrome, is seen in 3–20% of RCC patients. The syndrome is characterized by generalized hepatitis with lymphocytic infiltration, Hepato cellular degeneration and elevations in liver enzymes in the absence of hepatic metastasis and jaundice, although cases of reversible cholestatic jaundice without evidence of hepatic disease have also been reported.<sup>14,15</sup>

The pathogenesis is unclear. Some believe that the renal tumor secretes hepatotoxins or lysosomal enzymes that stimulate hepatic cathepsins or phosphatases, which leads to Hepato cellular injury; others suggest that tumor-secreted hepatotoxins lead to hepatocyte injury with subsequent activation of the immune system. The aberrant tumor production of interleukin-6, known to stimulate hepatic protein production, may also play a role.<sup>1</sup> Clinically, patients may present with Hepatosplenomegaly, fever, and weight loss. Stauffer's syndrome may precede other manifestations of RCC and is characterized by elevated alkaline phosphatase, transaminases, erythrocyte sedimentation rate, gamma-glutamyl transferase and prothrombin time.<sup>15</sup>

### Acknowledgements

None.

### Conflict of interest

The author declares no conflict of interest.

### References

1. Sacco E, Pinto F, Sasso F, et al. Paraneoplastic syndromes in patients with urological malignancies. *Urol Int.* 2009;83(1):1–11.
2. Trias I, Algaba F, Condom E, et al. Small cell carcinoma of the urinary bladder. Presentation of 23 cases and review of 134 published cases. *Eur Urol.* 2001;39(1):85–90.
3. Chasan SA, Pothel RL, Huben RP. Management and prognostic significance of Hypercalcemia in renal cell carcinoma. *Urology.* 1989;33(3):167–171.
4. Ding GX, Feng CC, Song NH, et al. Paraneoplastic symptoms: Cachexia, polycythemia, and Hypercalcemia are, respectively, related to vascular endothelial growth factor (VEGF) expression in renal clear cell carcinoma. *Urol Oncol.* 2012;31(8):1820–1825.
5. Turner JS, Cheung EM, George J, et al. Pain management, supportive and palliative care in patients with renal cell carcinoma. *BJU Int.* 2007;99(5 Pt B):1305–1312.
6. Turalic H, Deamant FD, Reese JH. Paraneoplastic production of granulocyte colony stimulating factor in a bladder carcinoma. *Scand J Urol Nephrol.* 2006;40(5):429–432.
7. Lin HC, Chai CY, Su YC, et al. Leukemoid reaction resulting from granulocyte colony-stimulating factor producing urothelial carcinoma of the renal pelvis. *Kaohsiung J Med Sci.* 2007;23(2):89–92.
8. Loughlin KR, Gittes RF, Partridge D, et al. The relationship of lactoferrin to the anemia of renal cell carcinoma. *Cancer.* 1987;59(3):566–571.

9. Nieken J, Mulder NH, Buter J, et al. Recombinant human interleukin-6 induces a rapid and reversible anemia in cancer patients. *Blood*. 1995;86(3):900–905.
10. Ok JH, Meyers FJ, Evans CP. Medical and surgical palliative care of patients with urological malignancies. *J Urol*. 2005;174(4 Pt 1):1177.
11. Wiesener MS, Munchenhagen P, Glaser M, et al. Erythropoietin gene expression in renal carcinoma is considerably more frequent than paraneoplastic polycythemia. *Int J Cancer*. 2007;121(11):2434–2442.
12. Nielsen OJ, Jespersen FF, Hilden M. Erythropoietin-induced secondary polycythemia in a patient with a renal cell carcinoma. *APMIS*. 1988;96(8):688–694.
13. Murphy GP, Kenny GM, Mirand EA. Erythropoietin levels in patients with renal tumors or cysts. *Cancer*. 1970;26(1):191–194.
14. Morla D, Alazemi S, Lichtstein D. Stauffer's syndrome variant with cholestatic jaundice: a case report. *J Gen Intern Med*. 2006;21(7):11–13.
15. Tomadoni A, Garcia C, Marquez M, et al. Stauffer's syndrome with jaundice, a paraneoplastic manifestation of renal cell carcinoma: a case report. *Arch Esp Urol*. 2010;63(2):154–156.