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Case Report

A Rare Paraneoplastic Syndrome That Presages a Poor Prognosis in Urothelial Carcinoma: A Case Report

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ABSTRACT

Isolated hypercalcaemia, leukocytosis or thrombocytosis is common in cancer patients, but the association of the first two is rarely described and the triple paraneoplastic syndrome is even more exceptional. Their concomitance portends a poor prognosis in solid tumor patients. We report the case of a 53-year old man with hypercalcaemia-leukocytosis-thrombocytosis paraneoplastic syndrome associated with a urothelial carcinoma which was fatal 4 months after diagnosis. Pathophysiology remains unclear but secretion of parathyroid hormone related protein (PTHrP) and cytokines such as granulocyte colony stimulating factor (G-CSF) as well as activation of thrombopoietin (TPO) receptor might be implicated. Although very rare, this paraneoplastic syndrome should be considered in solid tumor patients presenting with concomitant hypercalcaemia, leukocytosis and thrombocytosis, as it presages a poor prognosis with a rapid disease progression, and should be looked for and when present taken into account in the management of urothelial carcinoma, where no biological prognostic marker is available in clinical practice.

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Introduction

Bladder cancer is the ninth most common cancer worldwide and the most common malignancy involving the urinary system [1]. Urothelial (transitional cell) carcinoma accounts for approximately 90% of all bladder cancer histologic types and cigarette smoking is identified as the main risk factor [1]. Isolated hypercalcaemia, leukocytosis or thrombocytosis is common in cancer patients, but the association of the first two is rarely described and the triple paraneoplastic syndrome is even more exceptional [2-4].

Case Description

A 53-year-old smoker man with a newly diagnosed generalized high-grade invasive urothelial carcinoma was admitted to our Internal Medicine ward for the management of hypercalcaemia. Two months earlier, the patient had benefited from a right nephroureterectomy with partial cystectomy for urothelial carcinoma of the bladder infiltrating the distal right ureter staged pT3N0M0 (Figure 1A, 1B. and 2). A positron-

emission tomography-computed tomography (PET-CT) with fluorodeoxyglucose F18 (¹⁸F-FDG) performed 2 days before this admission revealed a massive peritoneal carcinomatosis with subcutaneous metastases, but no bone metastasis (Figure 3). Apart from hypercalcaemia at 3.71 mmol/L (normal value: 2.05-2.55 mmol/L), the laboratory tests showed a leukocytosis of 30.42x10³/mm³ white blood cell (WBC) (normal value: 4.00-10.00 x10³/mm³), a thrombocytosis of 638x10³/mm³ platelets (normal value: 150-400 x10³/mm³) and elevated C-reactive protein (CRP) of 76.6 mg/L (normal value: <5 mg/L). Despite no obvious cause of infection, the patient was treated with antibiotics until microbiological samples returned negative. In the work-up of hypercalcaemia, intact parathyroid hormone (PTH) was low (8 ng/L, normal value: 15-65 ng/L), and PTH related protein (PTHrP) was elevated (38,8 pg/mL, normal value: < 20 pg/mL). He was diagnosed with a hypercalcaemia due to a paraneoplastic secretion of PTHrP, which was treated with intravenous saline solution. The patient also received two courses of chemotherapy (Carboplatin-Gemcitabine) without human granulocyte colony stimulating factor (G-CSF) administration. Bisphosphonates were postponed because of poor oral hygiene and

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because calcaemia had decreased after the 2 courses of chemotherapy (but was not totally normalized). He left our inpatient department with a follow-up in the Oncology outpatient clinic. Ten days later he came back to the emergency department for confusion, fatigue, diffuse abdominal pain and nausea. Abdominal subcutaneous masses, already palpable during the previous stay, had increased in size and abdomen was painful and distended. Abdominal CT-scan confirmed an increase in metastases size (Figure 1C) Laboratory tests revealed a leukocytosis of $67 \times 10^3/\text{mm}^3$ WBC, mainly neutrophils ($60.5 \times 10^3/\text{mm}^3$) (normal value: $1.50\text{-}6.70 \times 10^3/\text{mm}^3$), a thrombocytosis of $693 \times 10^3/\text{mm}^3$ platelets, together with a massive hypercalcaemia of 5.05 mmol/L (Figure 4). No signs of infection could explain the leukocytosis and all microbiological

samples remained negative. A paraneoplastic leukemoid reaction (LR) was suspected and no antibiotics were given. Our patient still did not complain of any bone pain that could suggest bone metastasis. This time, as hypercalcaemia was severe and symptomatic, the patient received bisphosphonates (zoledronic acid) with a rapid decrease in its level (Figure 4). The increase of all three biological parameters at second admission (calcaemia, WBC count, platelet count, Figure 4) was correlated to the increase in tumor size radiologically and to the fast clinical deterioration. Eventually, due to the extremely rapid cancer progression despite chemotherapy, the low patient's performance status and according to his wish, he was transferred to palliative care and died 20 days after this second admission and 4 months after diagnosis.

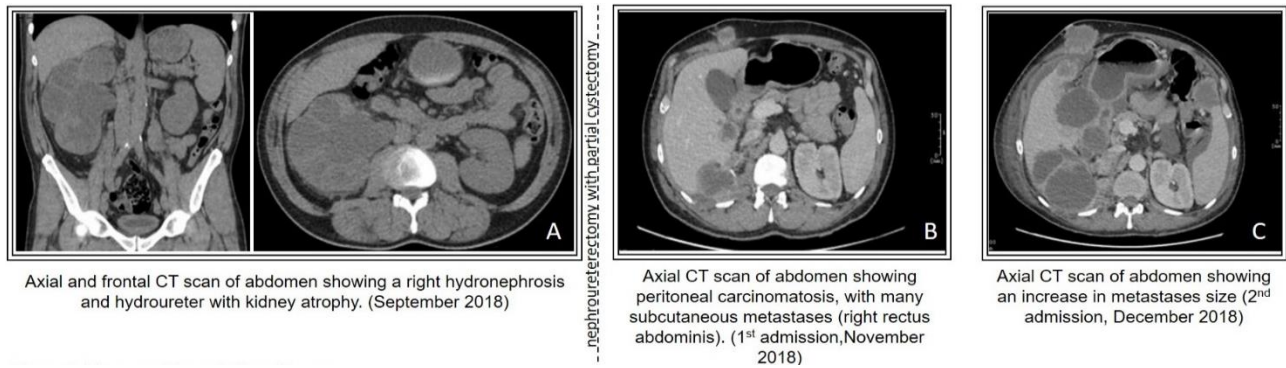


Figure 1: Tomography evolution of tumor.

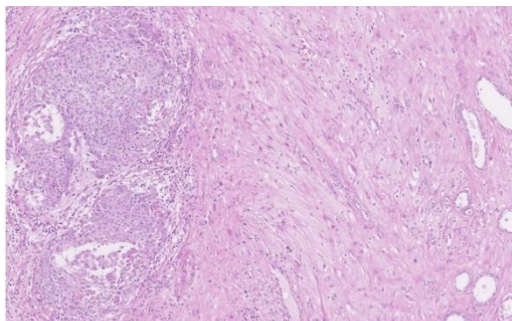


Figure 2: Histology of high grade invasive urothelial carcinoma.

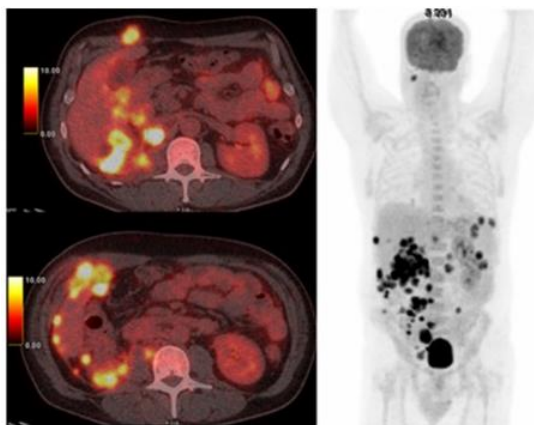


Figure 3: PET-CT ^{18}F -FDG.

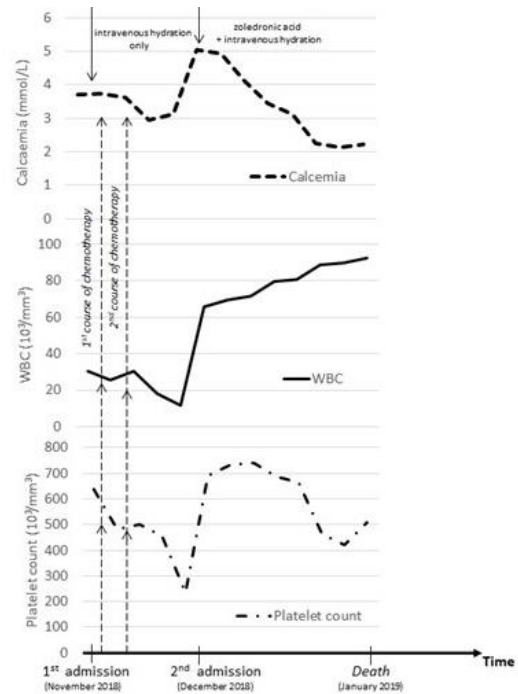


Figure 4: Evolution of calcaemia, white Blood Cell (WBC) and Platelet Count. Calcaemia normal value: 2.05-2.55 mmol/L, WBC normal value: $4.00\text{-}10.00 \times 10^3/\text{mm}^3$, platelet count normal value: $150\text{-}400 \times 10^3/\text{mm}^3$.

Discussion

Hypercalcaemia is common in patients with cancer, occurring in

approximately 20 to 30 % of cases [2]. There are two main mechanisms by which hypercalcaemia of malignancy can occur: osteolytic metastasis with local release of cytokines (~20 %) and tumor secretion of PTHrP (~80%) as described in this case [2].

A LR is defined by a leukocytosis with WBC count over $50 \times 10^3/\text{mm}^3$ and the diagnosis is based on the exclusion of chronic myelogenous leukemia (CML) and chronic neutrophilic leukemia (CNL) [3]. Malignancy-associated LR is commonly observed in a variety of carcinomas, especially in lung and kidney cancers [3]. In this case, as CML and CNL were highly unlikely and after exclusion of infection, paraneoplastic LR was considered.

Leukocytosis and hypercalcaemia are two of the most common paraneoplastic syndrome but association of both is rarely described and is particularly exceptional in urothelial carcinoma [5, 6-13]. In a series of 1149 lung cancer patients, Hiraki et al. studied hypercalcaemia and leukocytosis [5]. Their study revealed that 65 (5.7%) patients had hypercalcemia alone, 16 patients (1.4%) leukocytosis alone and only six patients (0.5%) both hypercalcaemia and leukocytosis. Survival in patients with hypercalcaemia-leukocytosis syndrome was significantly shorter ($P < 0.001$) than in patients without hypercalcemia and leukocytosis or with hypercalcemia alone, with a median survival time of 1.5 months. On the other hand, there was no significant difference in survival time between patients with hypercalcaemia —leukocytosis syndrome and patients with leukocytosis alone ($P = 0.47$).

In a large prospective study of 1410 patients with a histologic diagnosis of urothelial carcinoma, Izard et al. focused on paraneoplastic leukocytosis [6]. Nine patients (0.6%) presented with paraneoplastic leukocytosis (defined by WBC count over $20 \times 10^3/\text{mm}^3$ on 2 occasions separated by 30 days) and only 6 patients (0.4%) were diagnosed with hypercalcaemia-leukocytosis syndrome. Local and systemic therapies produced transient responses in some patients' WBC counts, followed by rapid recurrence of leukocytosis after cessation of the therapy, suggesting that the response could have been linked to the myelosuppression rather than to the tumoricidal activity. Other experiences suggest that recurrence of leukocytosis after local and systemic therapy is associated with clinical and radiological progression of the disease and could be the first sign of relapse after initial response to treatment.

Pathophysiology of this paraneoplastic syndrome remains unclear but secretion of PTHrP and cytokines such as G-CSF (a hematopoietic growth factor that causes leukocytosis) or other interleukine-mediated mechanisms might be implicated [5, 6]. In this case, G-CSF testing was not done because the patient's condition deteriorated rapidly. However, parallel evolution of calcaemia, WBC (Figure 4) and pejorative evolution of cancer seems to indicate that it is a paraneoplastic leukocytosis. Many different solid tumors can also enhance thrombocytosis, through cytokines production and TPO (thrombopoietin) receptor activation [4]. In our case, the parallel evolution of the platelet count, the WBC count, the calcaemia (Figure 4), the increase in tumor size (Figure 4.) and the rapid clinical deterioration suggests a common phenomenon.

Only 13 cases of urothelial carcinoma associated with hypercalcaemia-

leukocytosis syndrome were reported in the literature and to the best of our knowledge, less than 10 cases (including our patient) of urothelial carcinoma associated with hypercalcaemia-leukocytosis-thrombocytosis syndrome have been described [6, 13-15]. This triple association is thus rarer than the association of hypercalcaemia-leukocytosis, which is already known of poor prognosis [5]. Data is missing regarding the prognosis of the triple association, thus reports of cases are crucial for a better understanding of the phenomena.

Conclusion

Although very rare, this paraneoplastic syndrome should be considered in these patients presenting with concomitant hypercalcemia, leukocytosis and thrombocytosis, because it presages a poor prognosis with a rapid disease progression and the triple association should be looked for and when present taken into account in the management of urothelial carcinoma, where no biological prognostic marker is available in clinical practice.

Conflicts of interest

None.

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